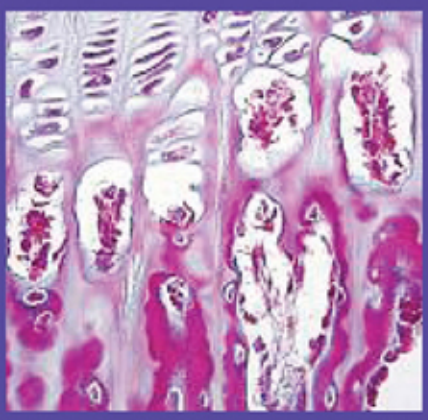
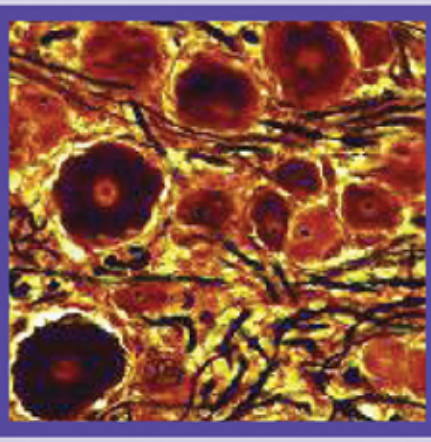
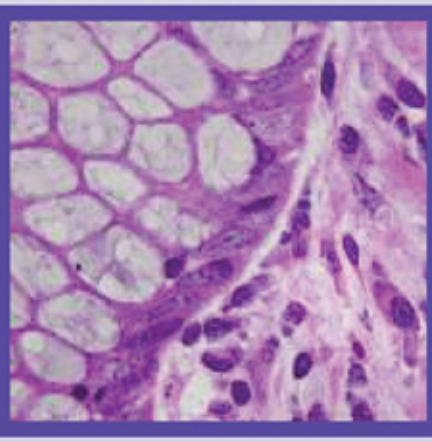
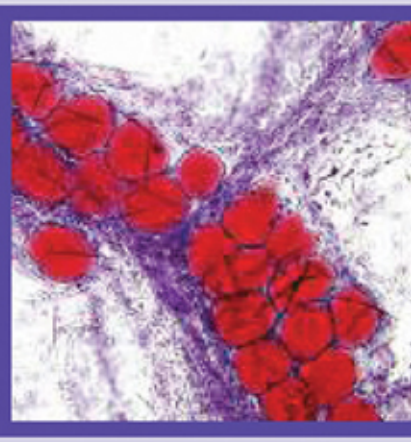
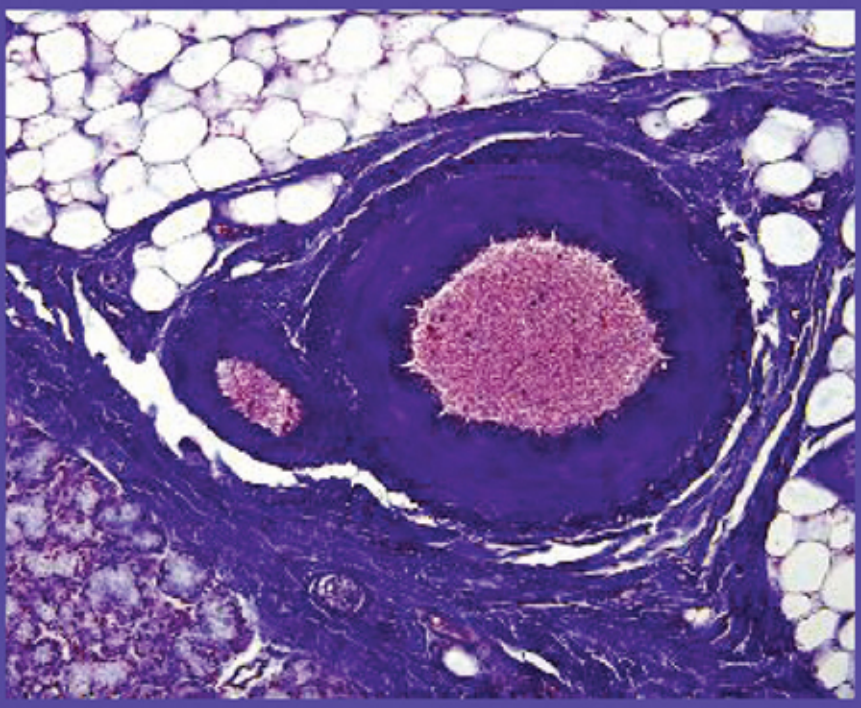
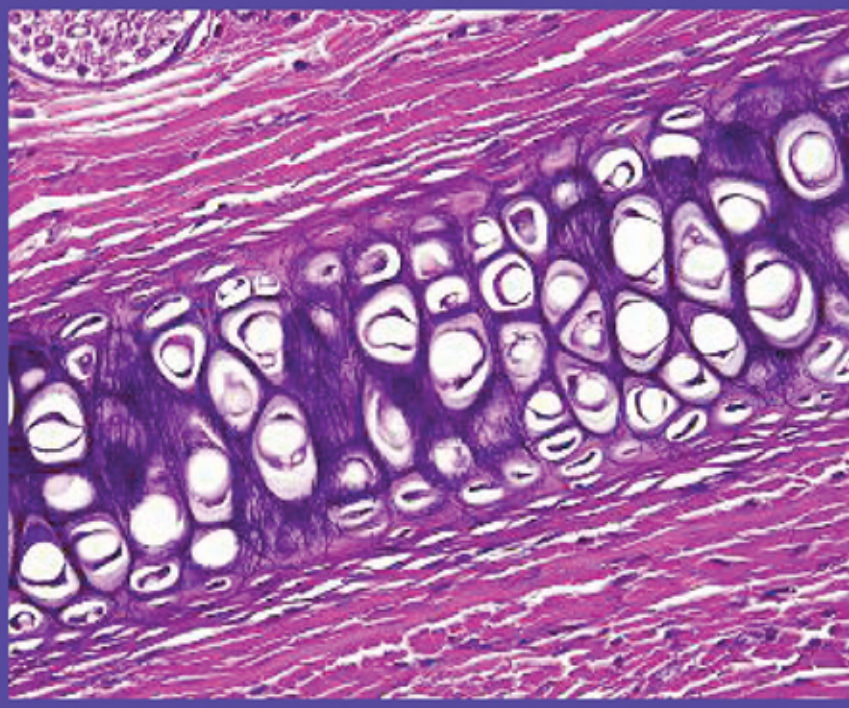





A Photographic Atlas *of* Histology

Michael J. Leboffe

A Photographic Atlas of Histology

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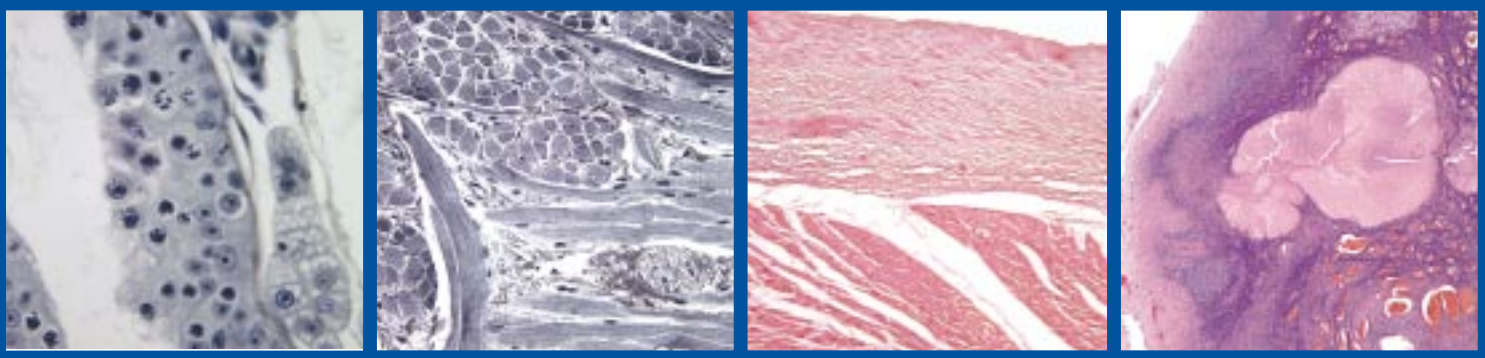
Preface



The primary goal and overriding theme of *A Photographic Atlas of Histology* is practicality. And while I expect that it will get used during home study and test review, I wrote with the student sitting at the microscope with a box of slides to examine in mind. My hope is that the images in this book will assist that student in identifying what needs to be seen. Toward this end, I used commercially available microscope slides to photograph, so the images represent the quality and diversity of what a student is actually likely to encounter in the laboratory; pathological specimens have not been used. I also have minimized the inclusion of electron micrographs, because beginning histology students are not typically required (or even allowed) to use an electron microscope. Finally, I wrote captions for the images as if I were showing projected images to a class, so they tend to be lengthy and descriptive.

The textual material is intended to be a concise synopsis of histological basics, not an exhaustive treatise on the discipline. Further, it is assumed the student has a basic background in anatomy, so gross anatomy is not covered. Neither is physiology discussed beyond a general description of function. You may want to examine other references that cover these topics in detail.

Histology is a challenging, but exciting discipline—once you develop certain skills. Beginners often dread spending hours over a microscope and then have difficulty "seeing anything." With practice and experience come a sharpened eye and strategies for successful examination of microscopic preparations, which make the process more rewarding. I have made some suggestions in Chapter 1 to quicken your arrival to this point. I encourage you to give them a try.

By the way, if you begin to imagine the cells are looking back at you, you've been studying too hard. It's time for a break.

I wish you success on your upcoming adventure.

Mike
San Diego, CA
January, 2003

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Acknowledgments

Even producing a book of modest size involves a tremendous amount of support, cooperation, and encouragement from many people. I would like to take this opportunity to publicly acknowledge them.

First, I want to express my gratitude and love to Karen, my wife of 25 years. Being the wife of an author was not part of the original deal, was it? Nevertheless, you continue to tolerate and love me through it all. You are the best. Next, thanks to our children who are both beneficiaries and victims of the writing process. Nathan (sorry, no need for hand models in this one!), Alicia, and Eric I appreciate how you have shared your dad with his career. I love you all and am proud of the people you are developing into. And yes, Alicia, I know I ended that last sentence with a preposition.

My "day job" is Professor of Biology at San Diego City College. Thanks to the other members of the Biology Department for their understanding and help as I served two masters during this project. In alphabetical order, thanks to Dianne Anderson, James Bartley, David Brady, Dr. Joyce Costello, Julie Haugsness-White, Dr. Khasha Khomejany, Burton Pierce, Debra Reed, Brett Ruston, Dr. David Singer, Dr. Minou Djawdan Spradley, and Gary Wisehart. Your direct and indirect contributions made this project go more smoothly and they, as you, are greatly appreciated.

The administration of San Diego City College continues to be supportive by making campus facilities available to me through the Civic Center Program. Thanks to Terrence Burgess, President, Ron Manzoni, Vice President of Instruction, Dr. Marianne Tortorici, Dean of Science, Nursing, Health and Athletics, and Carol Dexheimer, Business Manager for their support and cooperation.

It is safe to say that this project would not even have begun without the assistance of Bob Nazar of Olympus America, Inc. (www.olympus.com) and David McGhee of ImagingPlanet (www.imagingplanet.com). Bob made a state-of-the-art Olympus BX41TF photomicroscope with top of the line accessories available to me, while David provided the software and MagnaFire™ camera needed to capture the images digitally. Both also generously provided technical assistance when needed. You have my deepest gratitude.

Others who contributed are: J. Jesus Macias and Sylvia Macias (father and daughter, and both former students!) of the University of California, San Diego Medical Center generously supplied transmission electron micrographs throughout the book; Peggy Firth, medical illustrator, and Michael Arnold, graphic artist, produced original art work; Pamela Jandura, CBC of Leica Microsystems Inc. (www.leica-microsystems.com) provided the microtome photograph (Figure 1-1) and led me to John Yorston, Product Support Manager and Jack Vermeulen, International Marketing Manager, both of LEO Electron Microscopy, Ltd. (www.leo-usa.com) who provided Figures 1-4 and 1-6; Doreen Cantelmo and Stephanie Garguilo of Olympus America, Inc. supplied the photograph for Figure 1-2; Gary D. Wisehart photographed the bone cross section (Figure 5-13) and many years ago encouraged me to write in the first place—without your courage and ambition as a model, I wouldn't have undertaken this and other projects; and Laura Donahue and Bridget McCullough, students who supplied the blood for the hematocrit in Figure 6-1—you'll never know which one I used because I don't remember! Thanks to all of you.

Finally, my gratitude goes to Morton Publishing and the entire book production team you have assembled. This is my sixth project with Morton Publishing, and my experiences have been consistently positive. I have worked with Doug Morton, President and Chrissy Morton DeMier, Business Manager since 1995 and appreciate the confidence they showed in me when I proposed this project and the trust they demonstrated with basically an open-ended budget! (Can we sign a contract now?) New to me this time around was Biology Editor David Ferguson, a young, energetic and professional businessman. I appreciate your handling of the business matters and understanding that the creative process is difficult to rush. Joanne Saliger and her crew—Patricia Govro and Elaine McFarlane—at Ash Street Typecrafters, Inc. have done a marvelous job (again) of converting my partial thoughts, chicken scratches and last minute changes into an attractive product. Thanks also to Bob Schram of Bookends, Inc. for the cover and overall design. I'm proud to be associated with all of you and look forward to future projects.

With all this help, one might expect a perfect product, but experience has shown me that mistakes still slip through and I am ultimately responsible for them. If you have comments, suggestions or corrections, I encourage you to email me at mjpleb@netscape.net or contact me through Morton Publishing, http://www.morton-pub.com.

Thank you.

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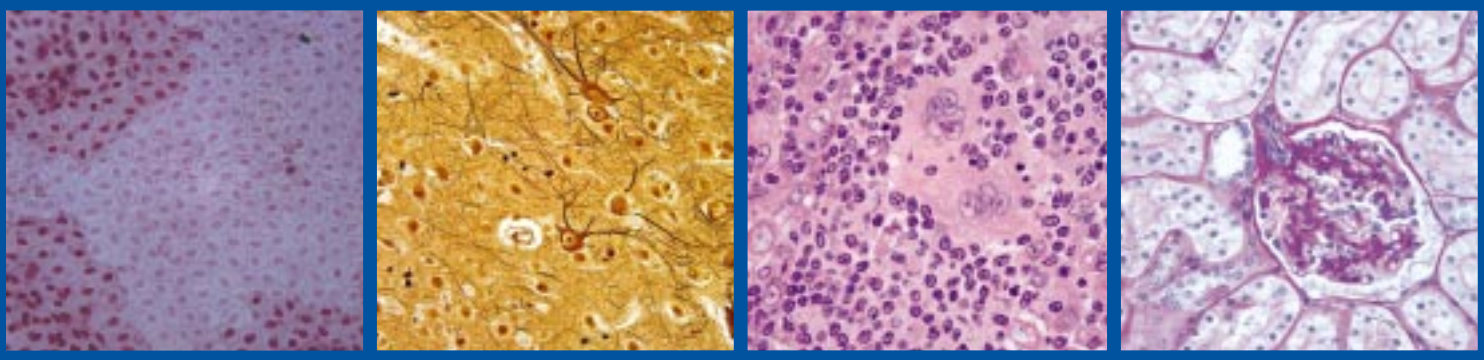

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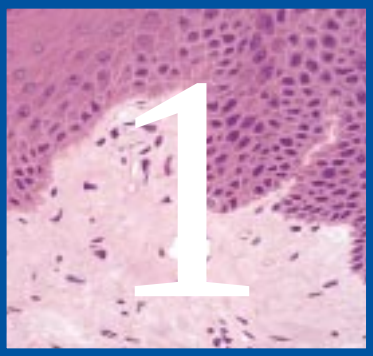
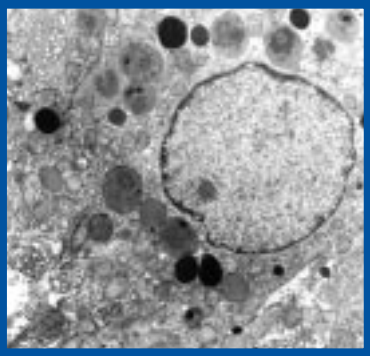
Introduction

CHAPTER 1

What is Histology?

Literally, histology is the study of tissues (*histos* = tissue; *logos* = treatise). Tissues are collections of cells that have a similar structure and function. In the adult, there are four major tissues:

- Epithelial tissue (epithelium)
- Connective tissue
- Muscle tissue
- Nervous tissue

In modern usage, the term histology has come to include all levels of microscopic anatomy—from tissues down to cells and cell ultrastructure, as well as the ways in which the tissues are combined to form organs and organ systems.

Why Study Histology?

Histology is the bridge between structure and function. It is at the microscopic level that we begin to see how an organ actually performs its functions. It is virtually impossible to discuss organ function without first considering its microscopic structure.

Histological Techniques—Specimen Preparation

In some cases, specimens may be examined immediately after removal from the body with staining as the only form of preparation. A blood smear would be an example. However, in addition to staining, most specimens must be prepared prior to observation. Preparation involves various chemical treatments, embedding with a supporting medium, and slicing into thin sections. An overview of the specific steps follows.

- **Fixation** The specimen is treated with a chemical fixative that alters its chemical composition and slows its deterioration. Chemical modification may include protein denaturation and cross-linking, and preservation of lipids and carbohydrates.
- **Dehydration** Beginning with a 50–70% alcohol solution, the specimen is bathed in successively more concentrated alcohol solutions (up to 100%) to remove water.
- **Clearing** Treatment with xylene makes the specimen transparent.
- **Embedding** The specimen is treated with a supporting medium, such as paraffin. (Paraffin is insoluble in water and alcohol but is soluble in xylene, thus making dehydration and clearing steps necessary.) First, the specimen is infiltrated with liquid paraffin, and then it is embedded in it as the paraffin is allowed to solidify. Plastics are sometimes used for embedding because they allow thinner sections (<1 µm) to be made.
- **Sectioning** The paraffin block containing the specimen is mounted on an instrument called a **microtome** (Figure 1-1). The microtome has a blade and a mechanism that moves the block a preset distance (usually 5–10 µm) after each cut. Thus, each time a cut is made, the paraffin block is moved a distance equal to the thickness of the next slice. In this fashion, many slices of uniform thickness are made.

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- **Mounting** Each slice is applied to a glass slide.
- **Staining** To provide contrast, specimens are colorized with various stains. The colored portion of some staining solutions is acidic. Acidic stains colorize basic (alkaline; positively-charged) cellular structures, which are said to be **acidophilic**. Basic stains are used to colorize acidic cellular structures, which are said to be **basophilic**. Hematoxylin and eosin stain (H&E) is used for most routine preparations and consists of a basic and an acidic component. The basic stain hematoxylin and the acid stain eosin produce the purple and pink specimens frequently encountered in a histology laboratory. Table 1-1 lists some common stains and the structures they highlight. Since most stains are aqueous solutions, the paraffin must be removed and the section rehydrated prior to stain application. Following staining, the specimen is again dehydrated and a cover slip is permanently mounted over it.

The whole process may take 48 hours to complete. For specimens that need to be examined quickly (as with surgical samples) the tissue may be sectioned using a freezing microtome. Freezing replaces the embedding process and makes dehydration and clearing unnecessary. Freezing microtomes are also used when lipids are to be examined in tissue because they are removed when treated with solvents such as xylene.

Preparation of specimens for electron microscopy is similar to preparation described above. The fixing solutions, such as osmium tetroxide, glutaraldehyde and potassium permanganate, act as electron-dense stains as well as serving the primary function of preserving the tissue. Tissues are typically embedded in plastic prior to being cut in sections 25 to 100 nm thick.

Histological Techniques—Microscopy

The **light microscope** (Figure 1-2) is used to examine specimens by *transillumination*, that is, by shining light through them. The **mechanical components** include **focus adjustments**, a **mechanical stage**, and a **light source**. The **optical components** include a **condenser**, **objective lenses**, and **ocular lenses**. The condenser concentrates the light and illuminates the specimen uniformly. Light from the specimen is **refracted** (bent) by the objective lens to produce a magnified image, which is then magnified again as it passes through the ocular lens and is transmitted to the retina of the eye. A sample light micrograph is shown in Figure 1-3.

The amount of magnification produced by each lens is marked on the lens. Total specimen magnification is the product of the power of the objective lens and the ocular lens. Since typical microscopes have 4x (low power), 10x (medium power), 40x (high dry power) and 100x (oil immersion) objectives and 10x oculars, the total magnifications are 40x, 100x, 400x, and 1000x, respectively.

Magnification is not the only important feature of a microscope. The ability to produce magnification with good **resolution** is what really matters. Basically, resolution is the ability of a lens to produce a clear image. Technically, it is the ability of a lens to see two separate points as being separate. The closer together the two points are when they can be seen as separate, the better the resolution of the microscope. The limit of resolution for light microscopes is about 0.1 µm, which allows production of quality images magnified up to about 1500x.

The **electron microscope** (Figure 1-4) uses an electron beam to create an image. The limit of resolution is improved by a factor of 1000 (theoretically down to 0.1 nm, but more realistically down to 2 nm) over the light microscope and the maximum magnification is about 150,000x. The **transmission electron microscope (TEM)** produces a two-dimensional image of an ultrathin section by capturing electrons that have passed through the specimen. The degree of interaction between the electrons and the heavy metal stain affects the kinetic energy of the electrons, which are collected by a fluorescent plate. The light of varying intensity produced is directly proportional to the electron's kinetic energy and is used to produce the image. The TEM is useful for studying a cell's interior, its **ultrastructure**. A sample transmission electron micrograph is shown in Figure 1-5.

A **scanning electron microscope (SEM)** is used to make a three-dimensional image of the specimen's surface. In this technique, a beam of electrons is passed over the stained surface of the specimen. Some electrons are reflected (*backscatter electrons*), whereas other electrons (*secondary electrons*) are emitted from the metallic stain. These electrons are captured and used to produce the three-dimensional image. A sample scanning electron micrograph is shown in Figure 1-6.

Strategies for Studying Histology

I took my first histology class in 1975 as a graduate student. My professor told us of a supplemental atlas (Di Fiore's *Atlas of Human Histology*, then in its fourth edition) that was available as a "crutch" if we needed it. After one lab period, I set my grad student pride aside and gladly purchased my crutch. At the time, I just thought it was me. However, teaching anatomy and histology for over 25 years has convinced me that this discipline is just plain difficult for most students to master. Nevertheless, "difficult" does not equate to "impossible" or "not worthwhile." Here are some tips that I hope will help you learn what you need to know.

- Read the slide's label. It will tell you what the specimen is, how it was sectioned (or if it is a "whole mount"), and often what stain was used.
- Realize that most slides have more on them than what the label says. One of the most difficult skills to acquire in histology is to find the "correct" part of the slide to examine.

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- Examine the slide without the microscope to get an idea of what the section looks like. Often, you can see a lot without magnification. It also should help you to "zero-in" on the area of the slide you want to examine because you can position the slide on the stage with the relevant part centered. (Remember that the specimen's image will be upside down and backward from its orientation on the stage.)
- Begin microscopic examination at low power. Get a feeling for what is on the slide and how the parts are related. When you see something of particular interest, center it and move to the higher powers.
- Do not over-illuminate the specimen. Using too much light results in loss of detail in the image. Reduce the light with the iris diaphragm to a point where you can still see the specimen, but it is not too bright. You will need to increase the light at each higher magnification to get the same degree of illumination since the field gets successively darker as higher power objectives are used.

TABLE 1-1 Commonly Used Histological Stains

STAIN	COMMENT
AZAN	*Stains nuclei, nucleoli and RBCs red, muscle orange, and connective tissue blue.*
AZURE B	*DNA is stained blue-green, RNA is stained purple.*
CRESYL VIOLET	*Typically a bacterial stain, it can be used to stain neuronal Nissl bodies purple.*
DAFANO SILVER METHOD	*Golgi material stains black.*
FEULGEN STAIN	*DNA is stained reddish violet.*
GIEMSA-WRIGHT STAIN	*Used for staining blood and bone marrow smears. Cytoplasm is stained light blue; cytoplasmic granules are either pink, purple or unstained; nuclei are dark purple.*
HEMATOXYLIN AND EOSIN (H&E)	*H&E is a very commonly used stain. Hematoxylin is a basic stain that colors acidic structures a purplish blue. These include the nucleus and regions with abundant ribosomes or rough endoplasmic reticulum, in addition to cartilage matrix. Eosin is an acidic stain and makes basic regions of the cell—that is, most of it—pink. It also stains collagen fibers pink.*
IRON HEMATOXYLIN	*This stains nuclei, chromosomes, mitochondria, centrioles, and muscle striations black.*
MASSON'S TRICHROME	*Results in three colors: basophilic structures are stained dark blue, collagen is stained green or light blue, and cytoplasm, keratin, muscle and erythrocytes are stained red.*
OSMIUM	*Stains lipid a dark brown color.*
PERIODIC ACID-SCHIFF (PAS)	*Colors complex carbohydrates red (magenta). Cells or cellular structures that stain red are said to be **PAS-positive**. Glycogen, brush borders, and the mucin in goblet cells are PAS-positive.*
SILVER STAIN	*Used for staining delicate structures, such as reticular fibers and neuronal processes.*
TRYPAN BLUE	*Phagocytic cells are stained blue when they engulf this dye.*

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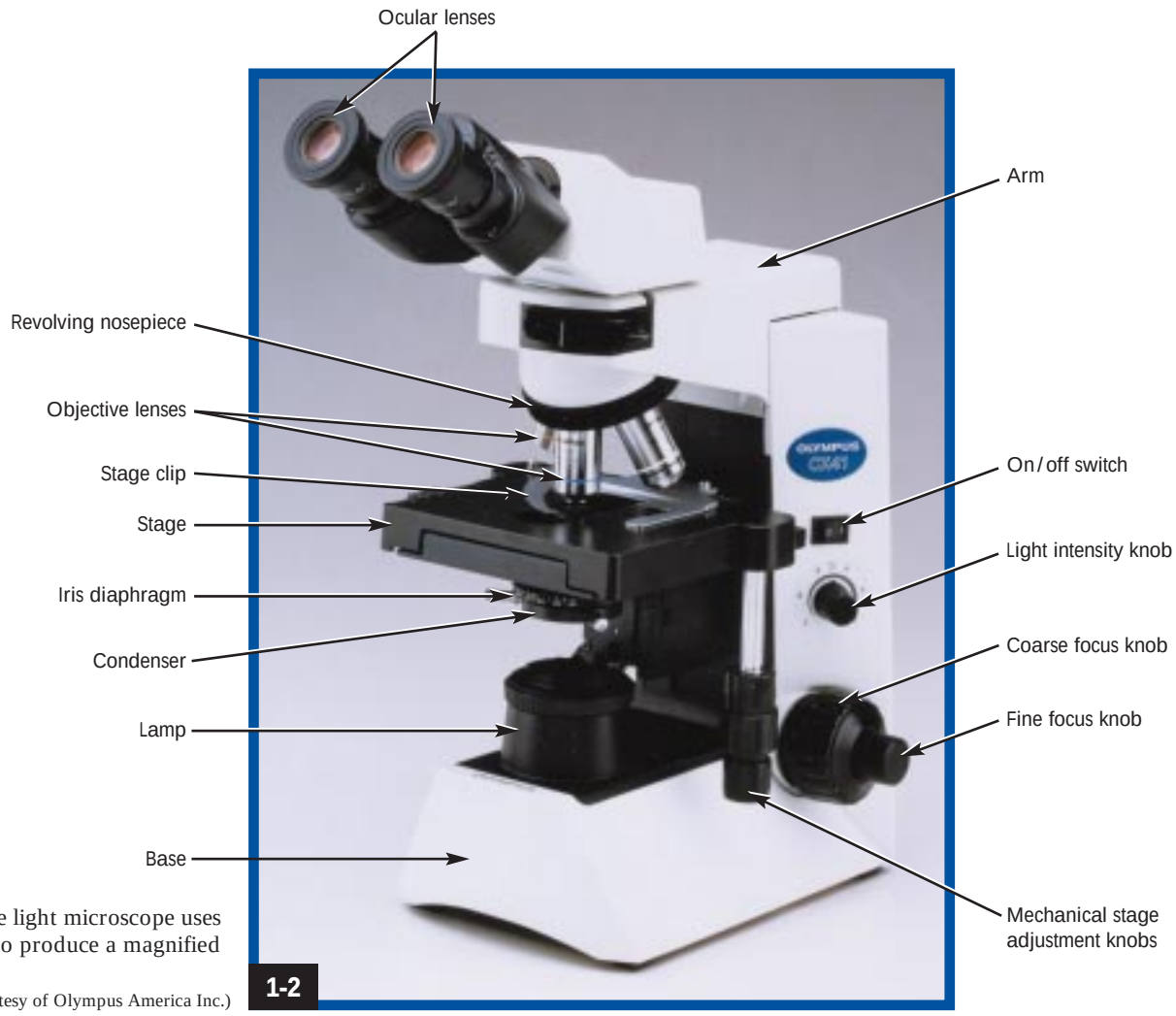
- This one may be the hardest. Don't be satisfied with looking at a single example of each assigned specimen. Look at several, then look at some more—especially if they are from a different organism or manufacturer. It takes examination of many examples before you will start to see the common construction.
- Most specimens have been cut into thin slices and you will be expected (eventually) to convert the essentially two-dimensional image you see on the microscope to a fully functional, three-dimensional object. This is equivalent to asking a person who has never seen a loaf of bread to imagine what the loaf looks like after examining a single slice. This skill will come with practice and by looking at three-dimensional drawings of the specimen as you examine it on the slide. So many structures are tubular, that it will also be useful to examine Figure 1-7 and see the many ways a tube appears depending on how it is cut.
- Don't overestimate slide quality. Photos in texts show good examples, but not every slide of an organ will show everything you need to see, and neither will slides necessarily be of uniform quality. In books such as this one, what you don't see are the dozens of slides, fields, and photographs that were discarded because of poor quality.

MICROTOME A microtome is used to make thin sections of specimens to be mounted on a microscope slide.
(Photograph courtesy of Leica Microsystems Inc.)



LIGHT MICROSCOPE The light microscope uses visible light and lenses to produce a magnified image of a specimen.
(Photograph courtesy of Olympus America Inc.)

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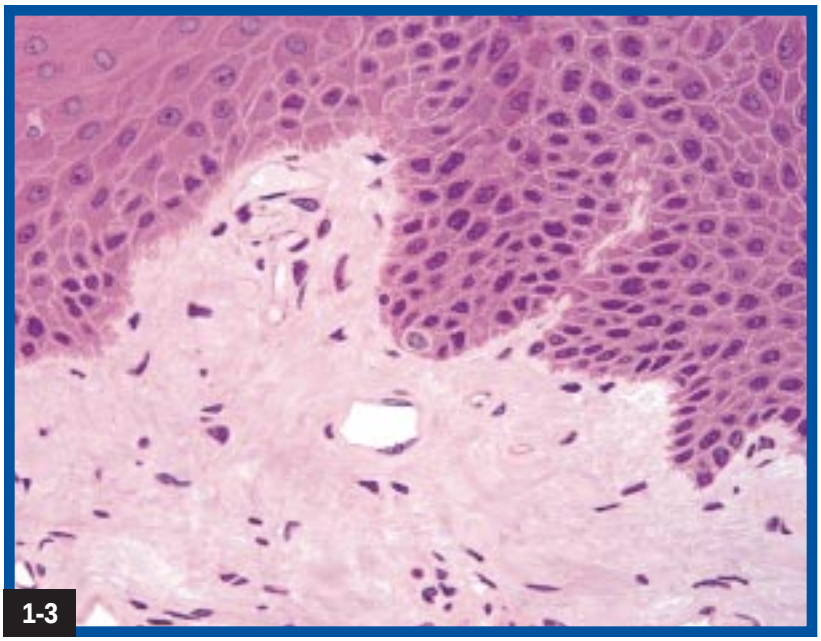

1-3

LIGHT MICROGRAPH A photograph of a microscopic image is a micrograph. This specimen from the skin was stained with H&E and magnified X600 by a light microscope.

1-4

ELECTRON MICROSCOPE The electron microscope produces an image using either transmitted electrons (TEM) or reflected electrons (SEM). The image is viewed on the monitor. Shown here is a research grade scanning electron microscope.
(Photograph courtesy of LEO Electron Microscopy Ltd.)

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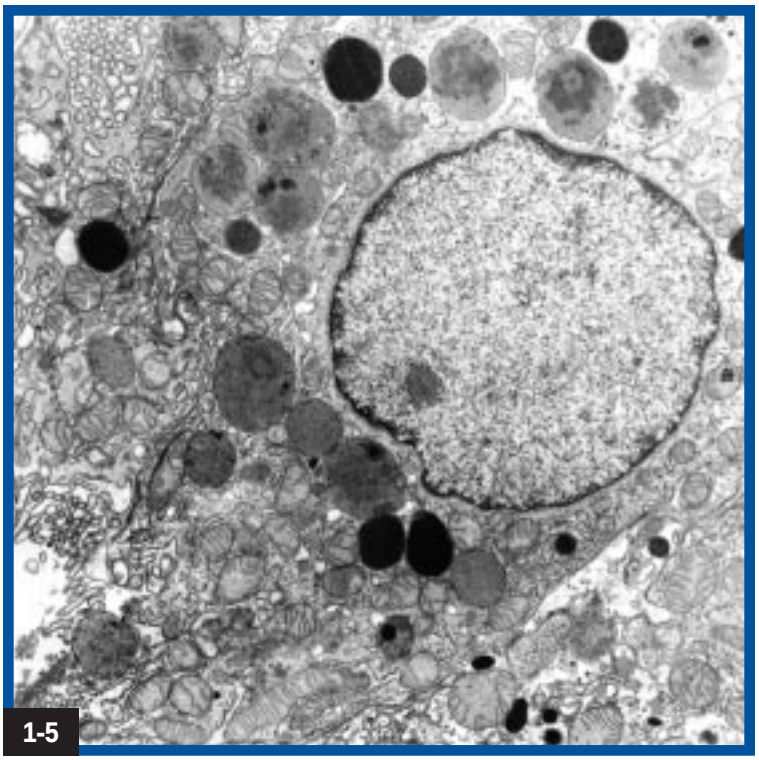

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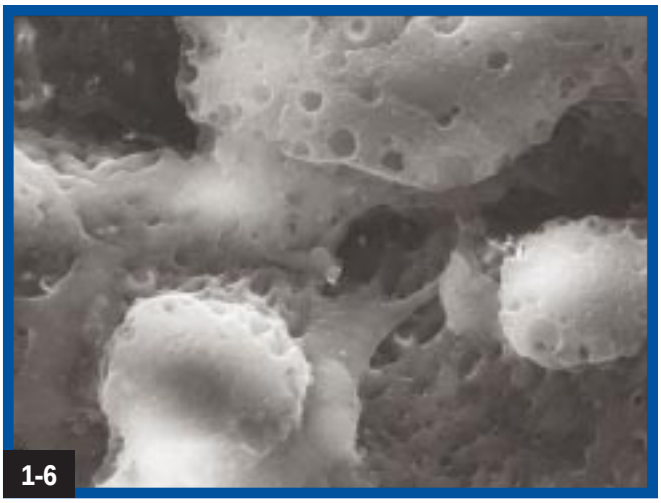
TRANSMISSION ELECTRON MICROGRAPH The TEM produces images of sectioned specimens. Since light is not used, the image is not in color. This cell was magnified X12,500.

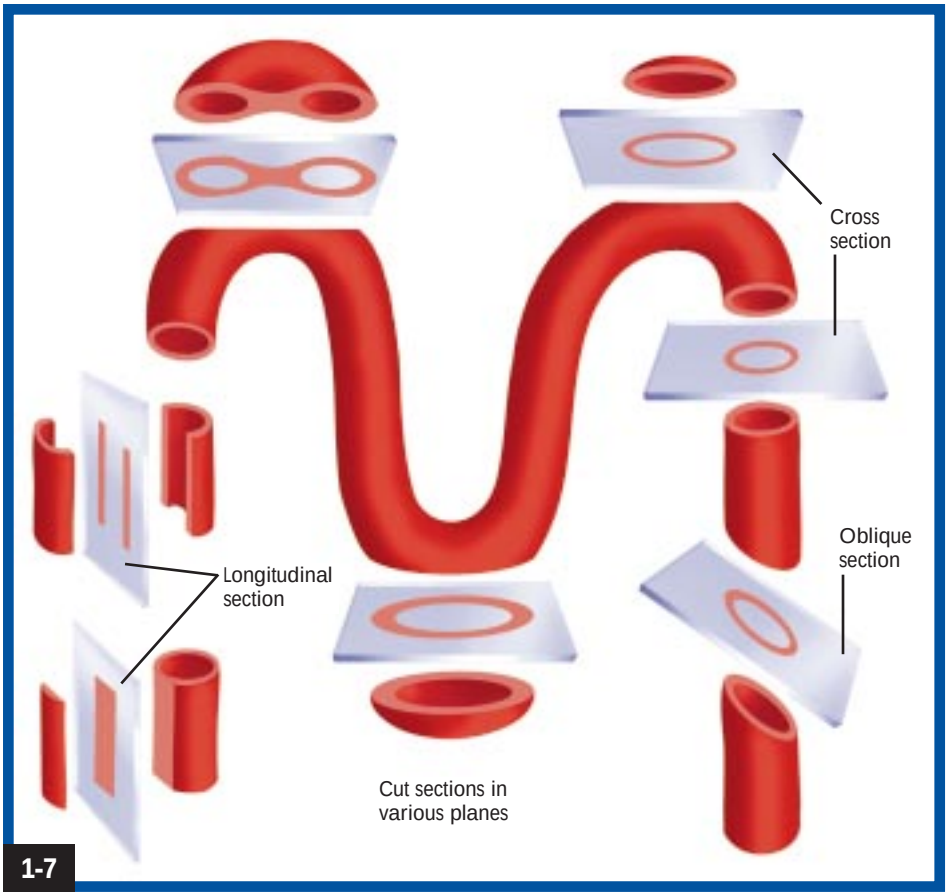
(Photograph courtesy of UCSD Medical Center.)



1-6

SCANNING ELECTRON MICROGRAPH Like the TEM, the image produced by the SEM has no color, but it is three dimensional. This specimen is from mouse liver and was magnified X1800.

(Photograph courtesy of LEO Electron Microscopy Ltd.)



1-7

SECTIONS OF A TUBE Study this diagram to gain an understanding of how the cut sections relate to the three dimensional whole. This is one of the toughest skills to learn as a histologist.

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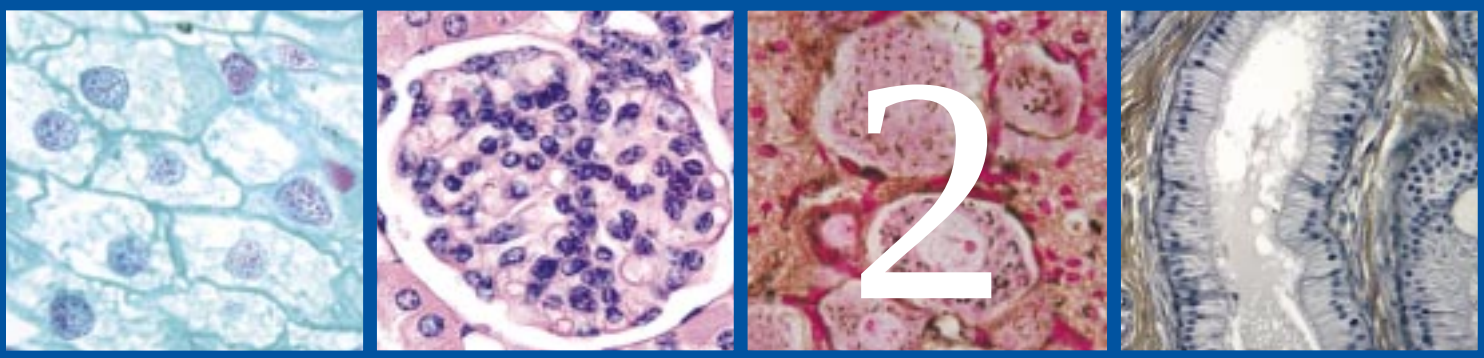
The Cell

CHAPTER 2



Tissues are made of cells, so it is appropriate to study cell structure and ultrastructure before embarking on a study of the tissues that comprise organs.

Cells were first discovered and studied using the light microscope. For centuries, our understanding of cell structure was based on the view provided by the light microscope. However, due to the physical limitations posed by using light to create the specimen's image, a point was reached where cell biologists had basically "seen it all." Figure 2-1 illustrates two light micrographs of cells stained with different dyes. Notice that the cells appear to be little more than granular cytoplasm surrounded by a membrane with a nucleus inside.

With the development of the electron microscope in the middle 20th Century and its ability to produce much higher magnification with greater resolution, cells could be visualized with a new degree of clarity. Structural detail (cell ultrastructure) that was inaccessible before was now revealed and opened the door to further study of cell structure and function. An artist's rendition of a generalized animal cell based on electron microscopy is shown in Figure 2-2.

While the electron microscope is used for most research applications, it is still the light microscope that is employed in introductory histology courses and routine examination of tissues in clinical settings. In this chapter, we briefly review cell ultrastructure as understood from electron micrographs, but the main emphasis is on what can be seen with the light microscope. For complete structural and functional details, the reader is referred to a standard reference text on general biology, histology, or cytology.

Cell (Cytoplasmic, Plasma) Membrane

While a line in the region of the **cell membrane** is often visible with the light microscope (Figure 2-3), it wasn't until the electron microscope was used that membranes could be visualized in detail. The electron microscope also revealed the presence of numerous membrane bound organelles in the cytoplasm.

Membranes are a double layer of phospholipids oriented with their hydrophobic fatty acid tails towards the interior of the membrane and the hydrophilic phosphate heads on each surface (Figure 2-4). Proteins are embedded in the phospholipid bilayer or are positioned on its surface. These proteins may be enzymes, transport proteins, receptors, electron carriers or form channels that penetrate the membrane. Other lipids and carbohydrates are also found in membranes. Functionally, the cytoplasmic membrane is the primary permeability barrier between the cell's interior and the external environment.

In electron micrographs, membranes appear as two dark lines separated by a lighter band in the center, with a total thickness of approximately 7 nm (Figure 2-5). While membranes throughout the cell have the same appearance, they differ in the particular phospholipids, proteins, and other components, depending on their functions.

Nucleus

The **nucleus** (Figure 2-1) is the most prominent cellular structure when viewed with the light microscope. It contains the cell's hereditary material—deoxyribonucleic acid (DNA). Each DNA molecule (of which there are 46 in

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a normal human cell) is composed of two long, thin polynucleotides wound in a double helix. Figure 2-6, which is stained to show DNA, gives no indication of the polymeric nature of the molecule, but does illustrate that DNA is localized in the nucleus. The genes of DNA contain information for production of cellular structures as well as the enzymes that catalyze metabolic reactions.

In a dividing cell, each DNA molecule and its associated proteins is tightly coiled and becomes visible as a **chromosome** (Figures 2-7 and 2-8). Chromosomes are an extremely compact and efficient form in which to distribute genetic material to the daughter cells produced by division (see the section on mitosis at the end of this chapter).

In a nondividing cell, the DNA is in a dispersed form called **chromatin**. Chromatin granules are often visible in light micrographs of the nucleus, especially at the periphery (Figure 2-9). Electron micrographs are able to differentiate between denser **heterochromatin** and less dense **euchromatin** (Figure 2-10). The former is inactive, whereas the latter is actively being transcribed into ribonucleic acid (RNA). In females, one entire X-chromosome is inactive and is sometimes visible in light micrographs as a "drumstick" at the periphery of the nucleus of certain white blood cells (Figure 2-11).

Also often visible in the nucleus are the **nucleolus** and **nucleoplasm** (Figure 2-12). The nucleolus appears as a dark region and is involved in rRNA synthesis. The nucleoplasm comprises the remaining contents of the nucleus.

Surrounding the nucleus is the **nuclear envelope**, often visible as a line in light micrographs (Figure 2-12), but shown to be a double layer of membrane in electron micrographs (Figure 2-13). The outer nuclear membrane is continuous with the rough endoplasmic reticulum. Regions in the nuclear envelope, called **nuclear pores**, are formed where the two membranes of the envelope join. Simple diffusion and ATP-dependent transport mechanisms move materials between the nuclear and cytoplasmic compartments of the cell through the pores.

Cytoskeleton: Thin Filaments, Intermediate Filaments, and Microtubules

The **cytoskeleton** is composed of protein filaments that are responsible for movement and maintaining cell shape. It is difficult to view with the light microscope, but in some cells where the filaments are especially abundant, its presence can be demonstrated (Figure 2-14).

Thin filaments (microfilaments) are composed of the protein actin. Actin filaments, along with the thicker myosin filaments, are present in skeletal and cardiac muscle where they form the contractile apparatus. While the individual filaments are not visible in light micrographs, their highly organized arrangement is reflected in the banding pattern seen in skeletal muscle fibers (Figures 2-15 and 2-16). Actin filaments are also involved in pinching the cytoplasm into two parts during cell division.

Electron micrographs show **microtubules** to be hollow protein cylinders. They form the interior of structures such as cilia and flagella (see page 9), comprise the **centrioles** of the **centrosome** (Figure 2-17), and are involved in movement of chromosomes during mitosis as the **spindle apparatus** (Figure 2-18).

Intermediate filaments are involved in maintaining cell shape and are intermediate in size between thin filaments and microtubules. In association with actin filaments and other proteins, intermediate filaments form the terminal web in the cytoplasm near the surface of epithelial cells. The cytoskeleton visible in Figure 2-14 is made primarily of intermediate filaments (neurofilaments).

Ribosomes

Ribosomes are small, electron-dense structures composed of ribosomal RNA (rRNA) and protein. In eukaryotes, the ribosome is made of a large subunit and a small subunit, distinguishable by their sedimentation coefficients (60S and 40S, respectively). Some ribosomes are attached to endoplasmic reticulum (Figure 2-19), whereas others are free in the cytoplasm (Figure 2-20). The former produce secreted proteins, whereas the latter are involved in synthesis of proteins for internal use. Ribosomes are not visible individually with the light microscope, but because of their RNA composition, they are basophilic. Many protein-secreting cells have a dark purple or blue cytoplasm due to the abundance of ribosomes (Figure 2-21).

Endoplasmic Reticulum

The cytoplasm of eukaryotic cells is traversed by a network of membranous tubules called **endoplasmic reticulum**. **Smooth endoplasmic reticulum (SER)** appears to be involved in steroid, cholesterol and triglyceride synthesis. The membranes of **rough endoplasmic reticulum (RER)** have ribosomes (Figure 2-19) involved in synthesis of proteins for external use. The endoplasmic reticulum is continuous with the outer nuclear membrane. The dark staining regions in the micrographs in Figure 2-21 actually show the regions of RER.

Golgi Apparatus

The **Golgi apparatus** (Figure 2-22) is made of a stack of curved, membranous sacs called **cisternae**. The Golgi is involved in carbohydrate synthesis, and modifying, sorting, and packaging proteins. The Golgi apparatus is visible with an appropriate stain or occasionally as a pale-staining region in the cytoplasm of some cells (Figure 2-23).

Mitochondria

Mitochondria (Figure 2-24) are double-membrane organelles that are the primary site of ATP production in the

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cell. The space bounded by the inner membrane is the **mitochondrial matrix** and possesses the enzymes of the Krebs cycle. Embedded in the inner membrane are the components of the mitochondrial electron transport system. Mitochondria are barely visible with the light microscope and appropriate stain.

Surface Modifications: Cilia, Flagella, and Microvilli

Cilia and **flagella** are easily viewed with the light microscope (Figures 2-25 and 2-26). Both are long, thin cellular projections involved in motility by producing sweeping motions. Typically, cilia are more numerous and shorter than flagella (which are found singly in humans). When viewed with the electron microscope, it was seen that both have the same basic construction. Both are surrounded by cell membrane and contain nine pairs of microtubules (doublets) around two single microtubules (singlets) (Figure 2-27). This 9+2 arrangement of microtubules constitutes the **axoneme**. At the base of each flagellum and cilium is a **basal body** composed of nine microtubule triplets with no central microtubules (identical to centrioles) into which the axoneme inserts.

Microvilli (Figure 2-28) are tiny projections that increase the surface area of cells involved in absorption. While not individually visible with the light microscope, they do appear as a **striated** or **brush border** on cells of the small intestine, colon, and kidney tubules (Figure 2-29). Actin filaments inside each microvillus anchor it to the terminal web.

Stereocilia are long microvilli found in the epididymis (Figure 2-30) and on the hair cells of the inner ear, where they are involved in producing a signal in response to sound waves.

Cellular Junctions

The first evidence that adjacent cells are connected by specialized attachments was provided by light micrographs of intestinal epithelium, which often exhibit **terminal bars** (Figure 2-31). The electron microscope has since revealed a number of structurally different types of attachments found not only in epithelium, but also in cardiac and smooth muscle. These include the following:

- **occluding** or **tight junctions** that bind adjacent epithelial cells tightly and seal the intercellular spaces; also known as **zonula occludens**
- **adhering junctions** which include **zonula adherans**, a continuous ring of attachment, and **desmosomes** which are spot attachments,
- **communicating** or **gap junctions** are made of tiny pores through which adjacent cells can transfer materials.

In epithelia, these collectively form the **junctional complex**. **Intercalated discs** (Figure 2-32) of cardiac muscle have been shown to be made of highly interdigitated cell membranes and junctions resembling zonula adherans, desmosomes, and gap junctions.

Cellular Inclusions

Some cells are specialized to store carbon and energy as either lipid or glycogen. These materials can be demonstrated with special stains. Figure 2-33 shows cells storing lipid and glycogen.

The Cell Cycle and Mitosis

The **cell cycle** marks the events of a cell between the time it comes into existence until it divides into two new cells. These events are divided into two major parts: **interphase** and **mitosis/cytokinesis**. Interphase (Figure 2-34a) comprises the majority of the cell cycle and is recognized histologically by a typically appearing nucleus. It is subdivided into three stages: **G_1 (first gap) phase**, **S phase**, and **G_2 (second gap) phase**. During G_1, the cell grows and begins synthesizing macromolecules necessary for DNA replication, the hallmark event of the S phase. The G_2 phase is devoted to synthesis of materials necessary for division.

Mitosis is the part of the cell cycle where replicated nuclear material is distributed to opposite ends of the cell prior to division of the cytoplasm, **cytokinesis**. In this way, the two daughter cells receive complete and identical amounts of nuclear DNA. Mitosis is divided into five stages.

- The first is **prophase** (Figure 2-34b), in which the chromatin condenses into visible chromosomes, nucleoli disappear, and the spindle apparatus (made of microtubules) begins to form. At this point, the chromosomes each possess two **sister chromatids** attached at a **centromere**.
- During **prometaphase**, the nuclear envelope disintegrates and the spindle fibers attach to each chromosome's centromere.
- During **metaphase** (Figure 2-34c), the chromosomes are positioned at the cell's equator to form the **metaphase plate**.
- In **anaphase** (Figures 2-34d and 2-34e), centromeres split and sister chromatids move to opposite poles of the cell.
- Mitosis ends with **telophase** (Figure 2-34f), in which the events of prophase are undone: chromosomes disperse as chromatin, the nucleoli reappear, the spindle apparatus disintegrates, and the nuclear envelope reforms.

During late anaphase and telophase, cytokinesis begins with the formation of a **cleavage furrow** (Figure 2-34g). The cleavage furrow eventually pinches the cytoplasm into two separate compartments—the daughter cells—and the division is complete.

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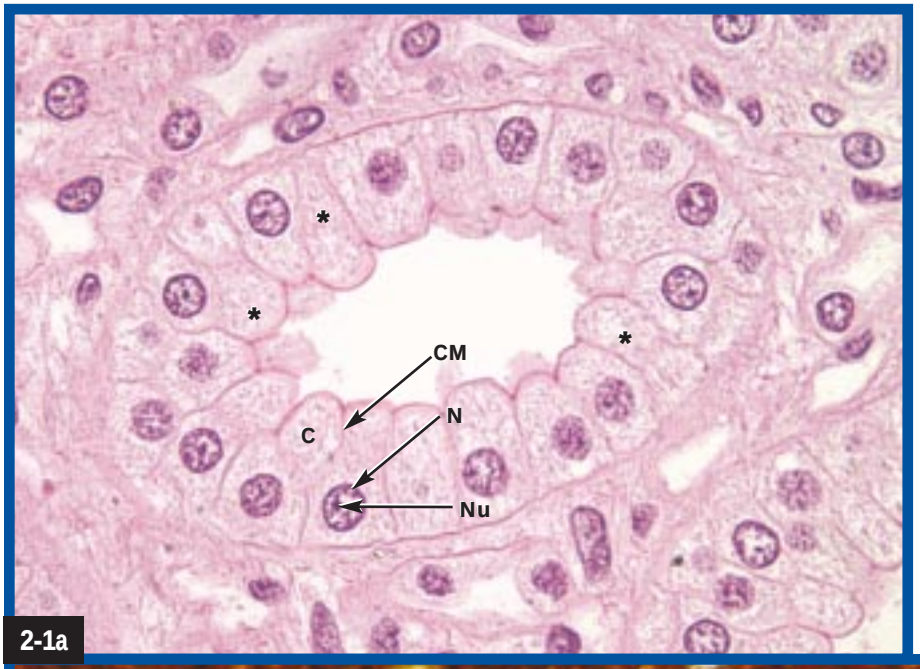
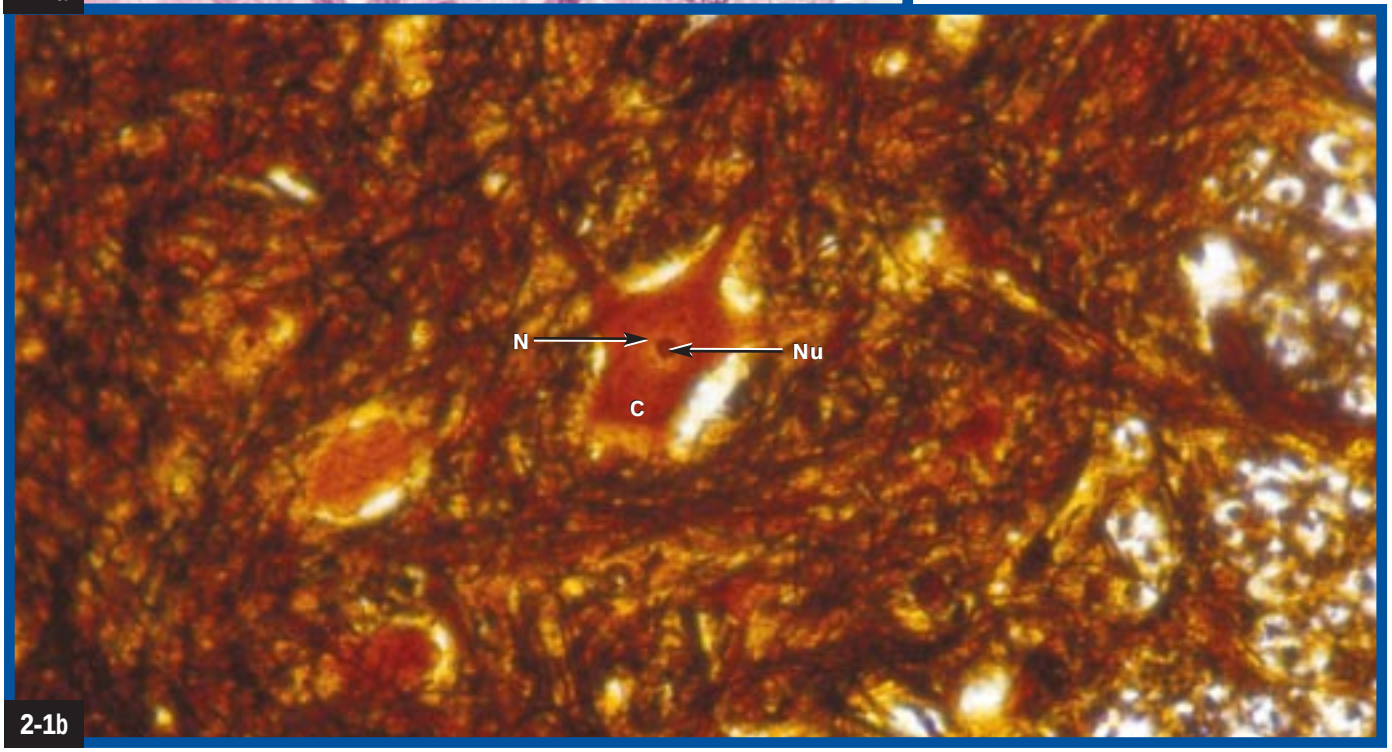
The specimens used to illustrate the stages of mitosis in Figures 2-34b through 2-34f were prepared exclusively for that purpose, but mitotically-dividing cells may be observed in various tissues (Figure 2-35). However, the cell cycle is not uniform for all body cells. Some cells continually divide, entering G_1 of interphase immediately following completion of mitosis/cytokinesis. Skin cells and the intestinal epithelium are examples. Others, such as liver cells, enter a **G_0 phase** and divide only when disease or damage make it necessary. **Terminally differentiated cells**, such as neurons, have become so specialized that they have lost their ability to divide.

Some cells in mitotically active tissue might not present chromosome arrangements that fit the defined categories. In some instances, it may be difficult to differentiate between late anaphase and early telophase, for instance. This is to be expected, since mitosis is a continuous process and we see the cells stopped in the middle of their activity. Further, the orientation of the division plane may complicate interpretation. Figure 2-34h shows a cell whose division plane is parallel with the page, so we are observing it from one end, not above. This makes placing it in a particular stage very difficult.



2-1a



2-1b

CELLS AS VIEWED WITH THE LIGHT MICROSCOPE (a) This light micrograph, stained with H&E, allows identification of cell membranes (CM), nuclei (N), and nucleoli (Nu), but the cytoplasm (C) just appears as a grainy, amorphous material. Notice the cells that apparently lack a nucleus (*). Their nuclei were not in the plane of the section so they appear to be absent. (*X600*) (b) A silver stain was used to prepare this specimen from the spinal cord. In it, the neuron's nucleolus is the most prominent feature with the nucleus staining lighter than the cytoplasm. *(X250)*

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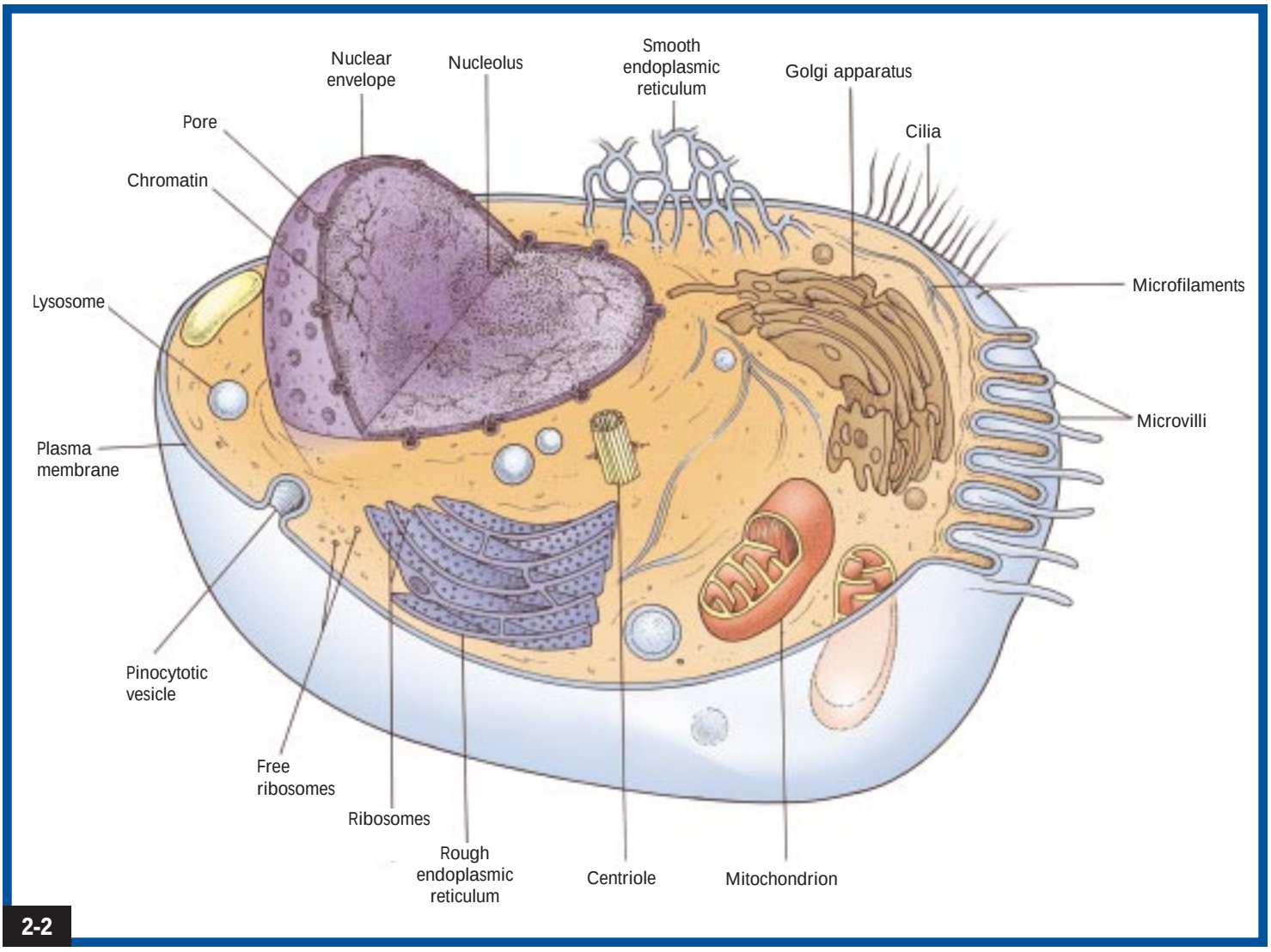
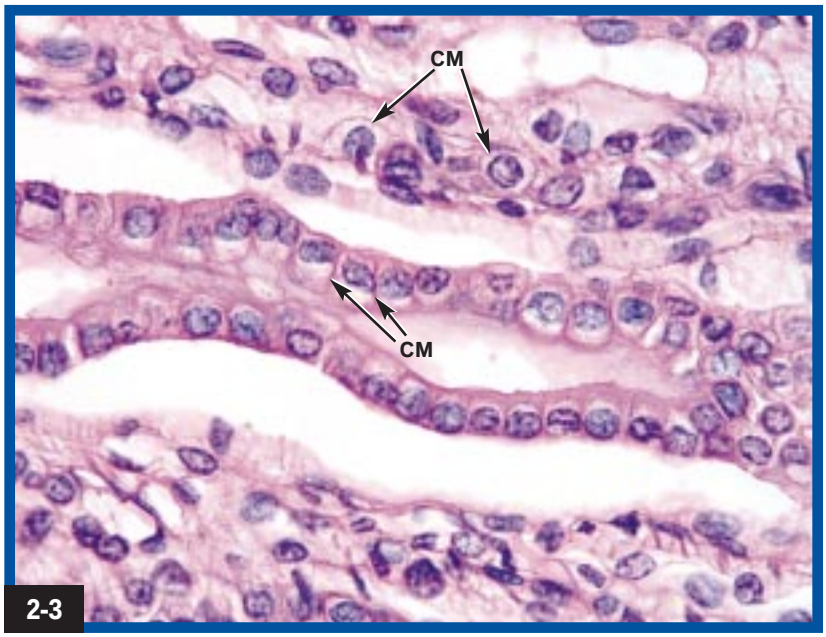


2-2

AN ARTIST'S RENDITION OF ANIMAL CELL ULTRASTRUCTURE This illustrates the general features found in animal cells, but not all would be seen in a single cell.



2-3

CELL MEMBRANE AS SEEN WITH THE LIGHT MICROSCOPE Membranes (CM) are pretty obvious between the cells of the tubule running across the field, but they are less distinct on many of the other cells in the field. *(X530)*

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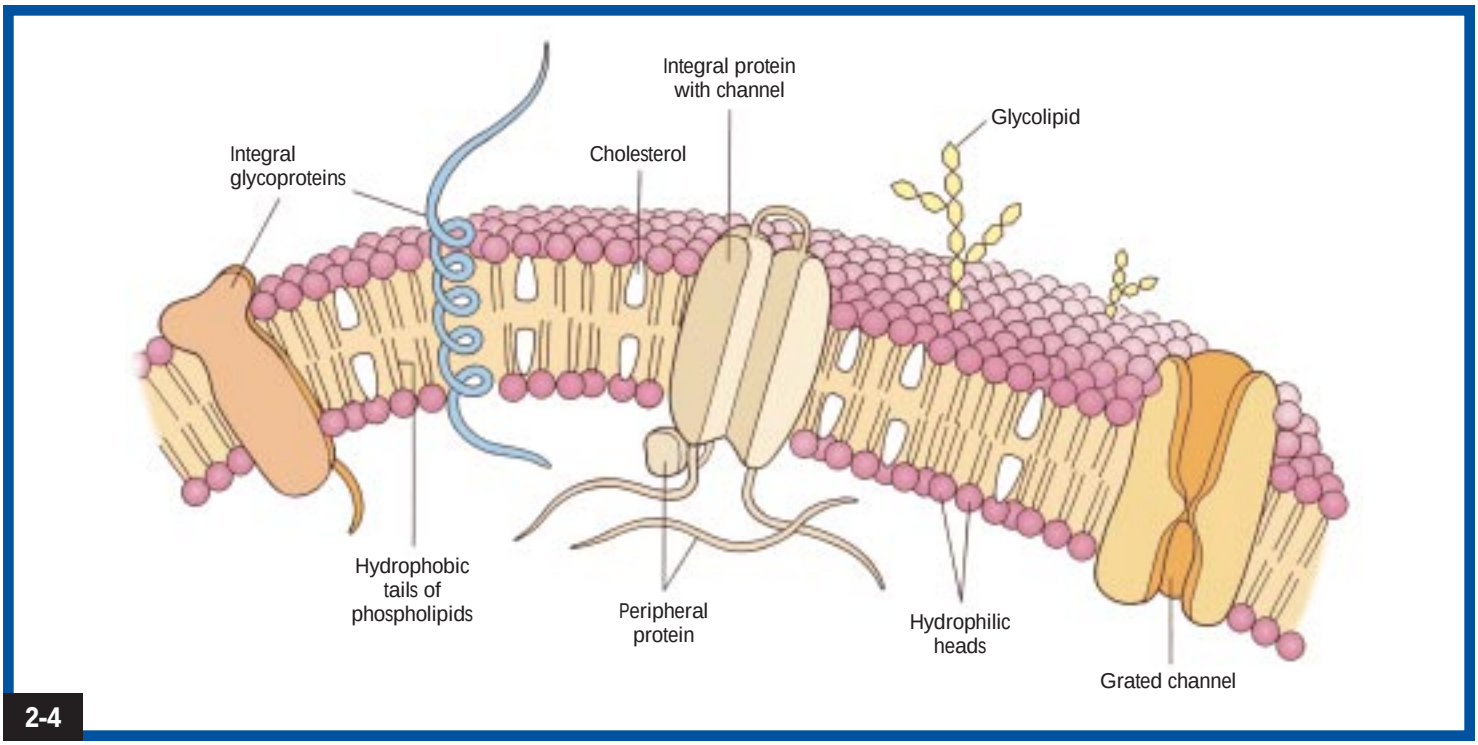
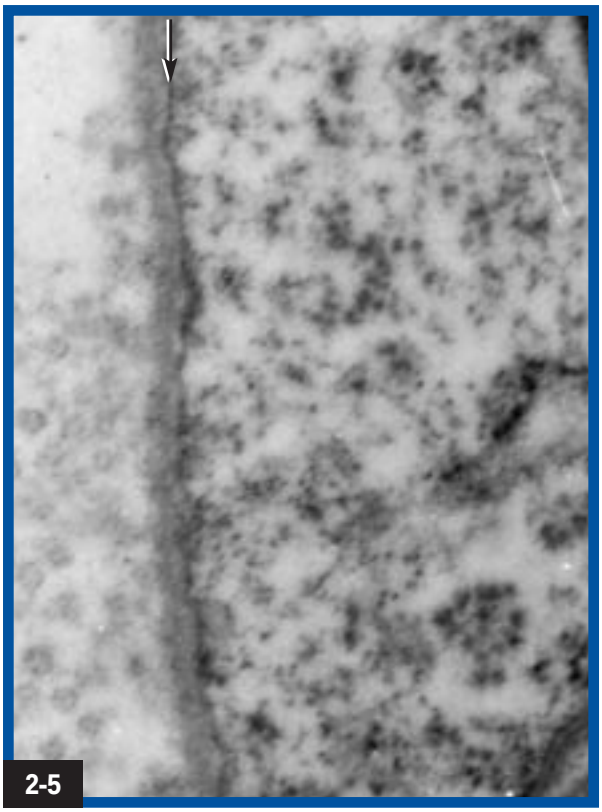


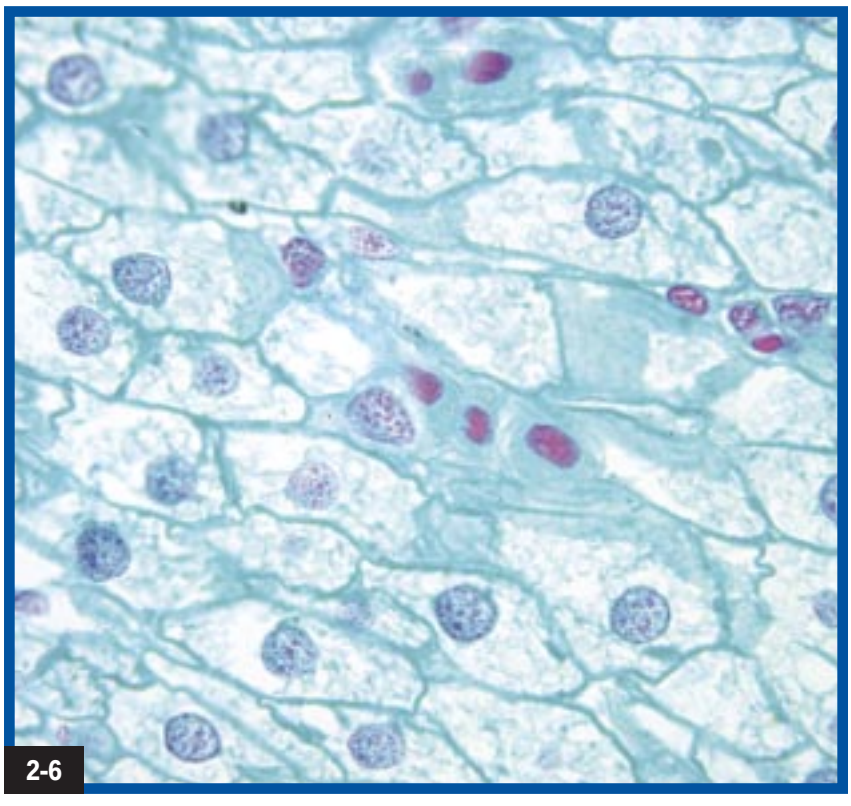
2-4

AN ARTIST'S RENDITION OF A TYPICAL MEMBRANE Membranes are composed of a phospholipid bilayer associated with various proteins and carbohydrates. The specific molecules and their locations are related to the membrane's function. Notice the orientation of the phospholipids, with their hydrophilic heads on each surface and their hydrophobic tails projecting to the membrane's interior.



2-5

ELECTRON MICROGRAPH OF A MEMBRANE In this TEM, the membrane (arrow) looks like a black line. At higher magnification, membranes typically appear as two dark bands surrounding a lighter band on electron micrographs. (*X140,000*) (Courtesy of UCSD Medical Center)



2-6

DNA STAIN DNA appears reddish when treated with a Feulgen stain. Notice that the DNA is found in the nuclei. (*X300*)

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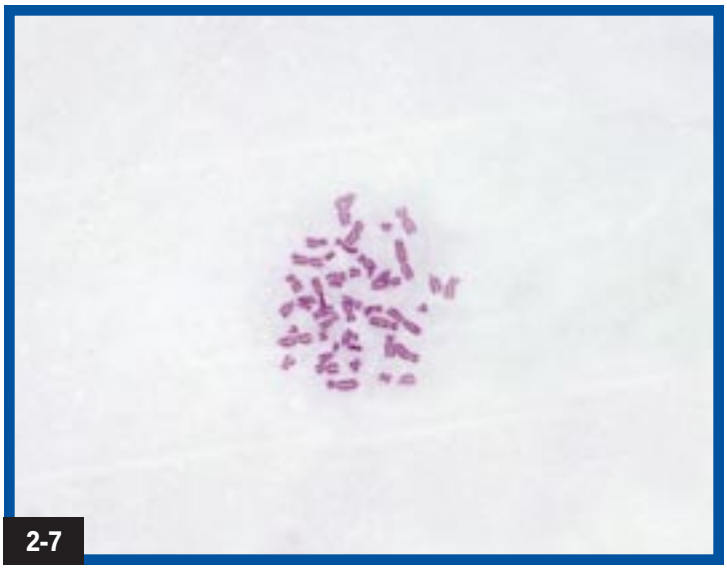
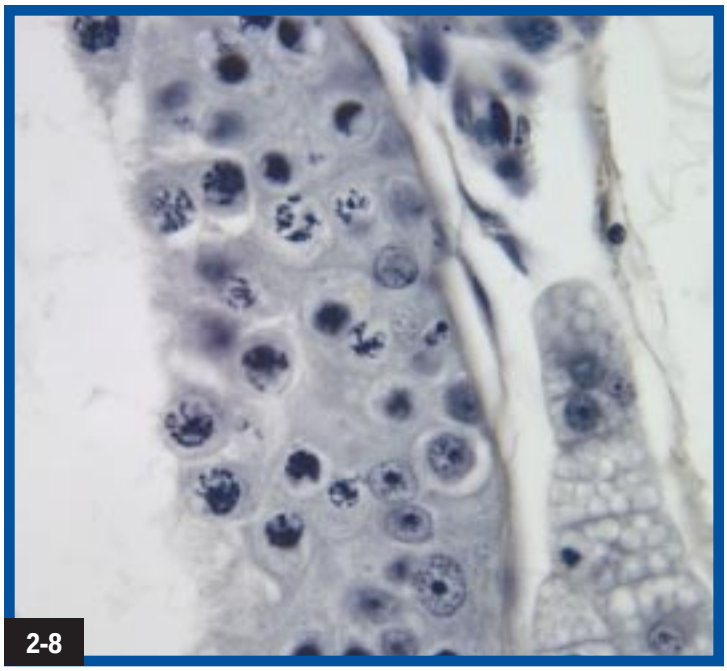


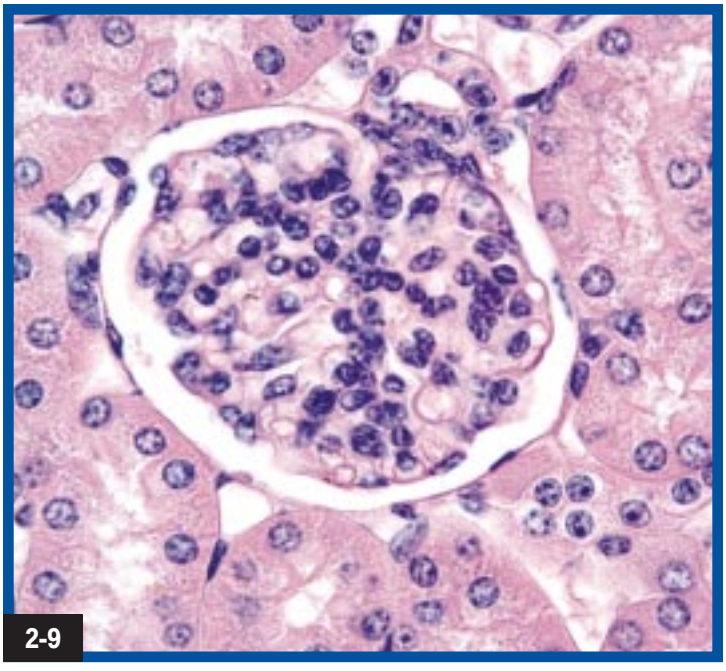
2-7

CHROMOSOME SPREAD Chromosomes are compact structures that are an efficient way of distributing the long DNA molecules to the two daughter cells during division. They are not visible during most of the cell cycle. These chromosomes are from a male cell grown in tissue culture. *(X650)*



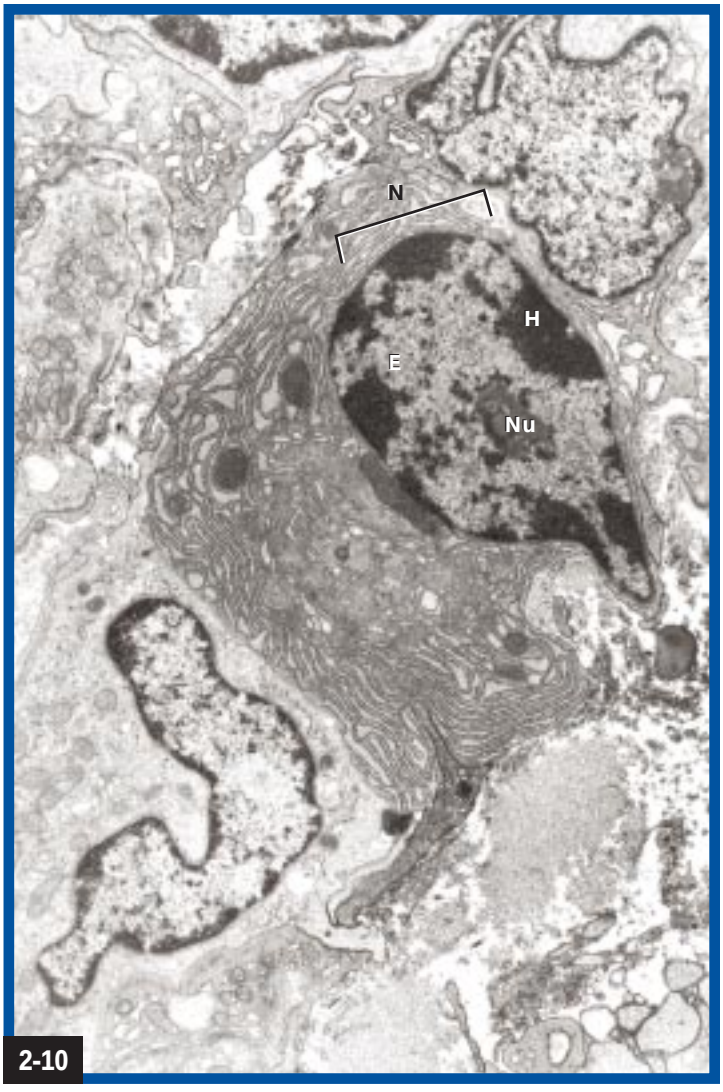
2-8

CHROMOSOMES Chromosomes are visible in tissues where the cells are actively dividing, as in these cells from the testes. *(X650)*



2-9

CHROMATIN GRANULES Dense regions of chromatin in the nucleus are often visible in light micrographs and may be of use in cell identification. *(X530)*



2-10

EUCHROMATIN AND HETEROCHROMATIN In this transmission electron micrograph, dense regions of inactive chromatin, called heterochromatin (H), are visible at the periphery of the nucleus (N). DNA that is being transcribed forms the lighter euchromatin (E). The medium gray region near the center is the nucleolus (Nu). *(X6,000)*

(Courtesy of UCSD Medical Center)

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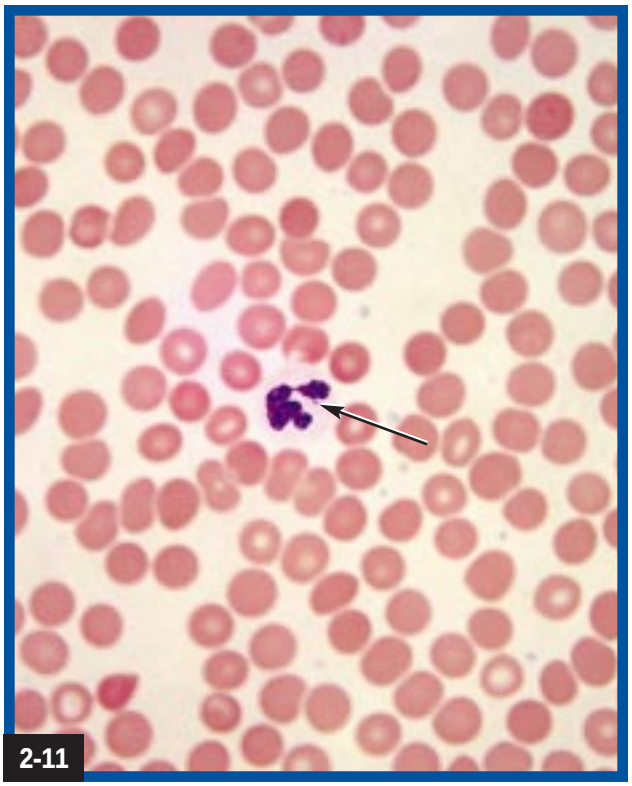
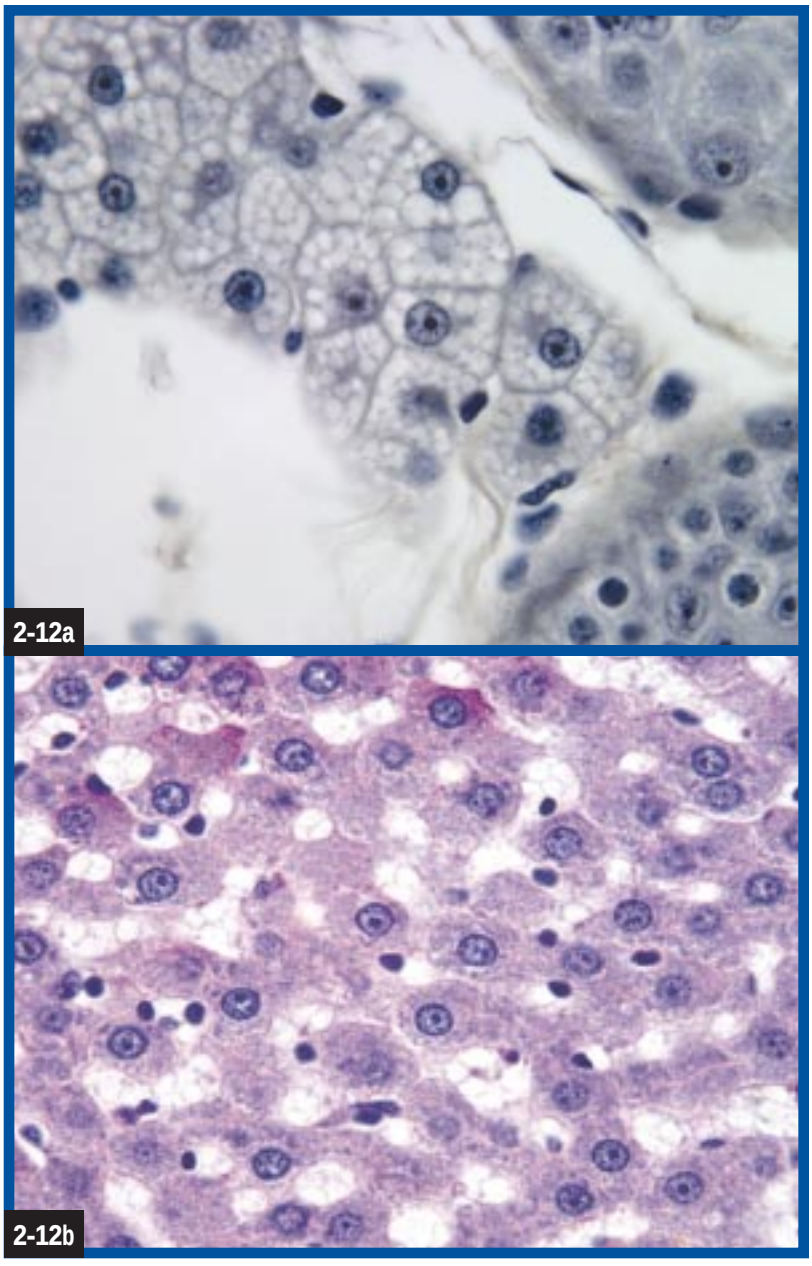


2-11

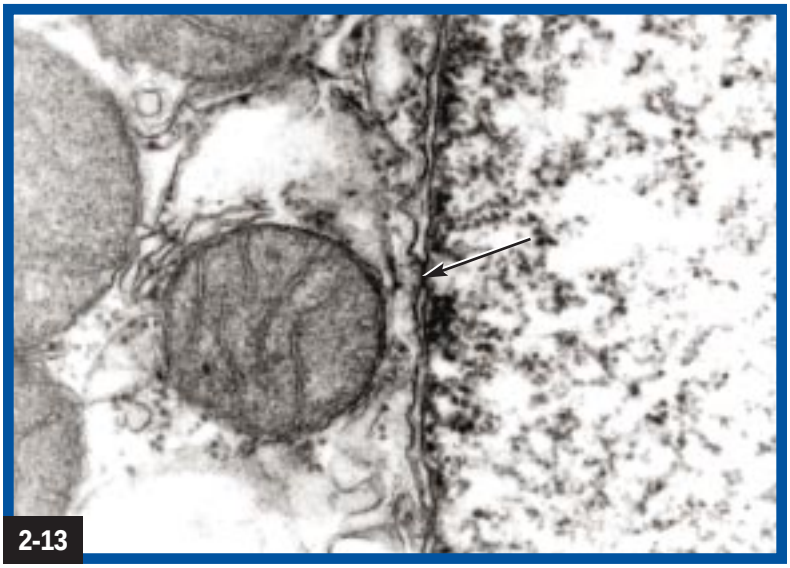
A "DRUMSTICK" The inactive X-chromosome in females is often visible as an appendage (arrow) of the nucleus in white blood cells called neutrophils. *(X650)*



2-12a

2-12b

NUCLEOLUS AND NUCLEOPLASM The nucleolus is a prominent dark region in light micrographs of the nucleus. It should not be confused with chromatin granules, which are usually toward the periphery. The nucleoplasm is the lighter, background material in the nucleus. The nuclear envelope is also visible as a dark line on the outside of the nucleus. (a) Testicular interstitial cells. (*X650*) (b) Liver cells. *(X650)*



2-13

NUCLEAR ENVELOPE AND PORES In this transmission electron micrograph, the nucleus is toward the right and the cytoplasm is toward the left. The double membrane of the nuclear envelope runs vertically in the center of the field. A nuclear pore is also visible (arrow). (*X31,500*)

(Courtesy of UCSD Medical Center)

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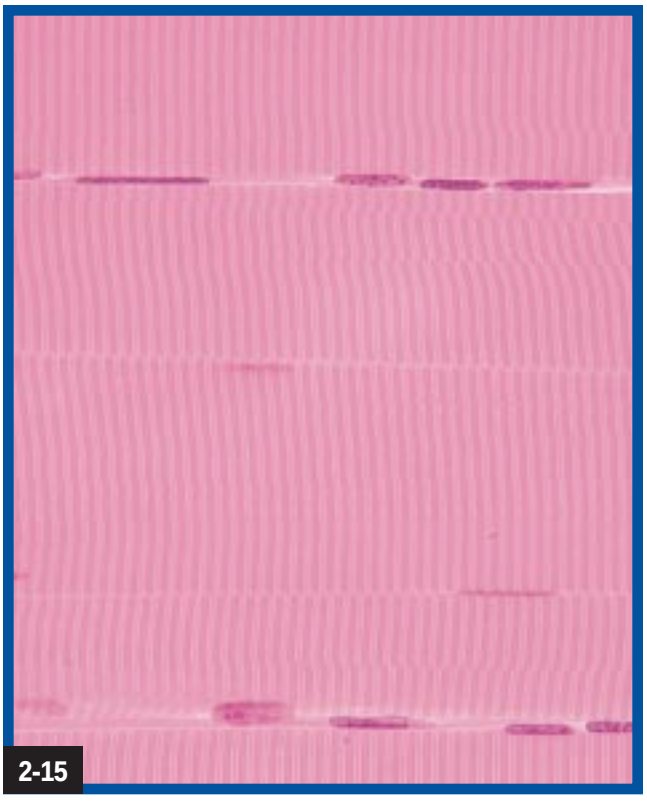
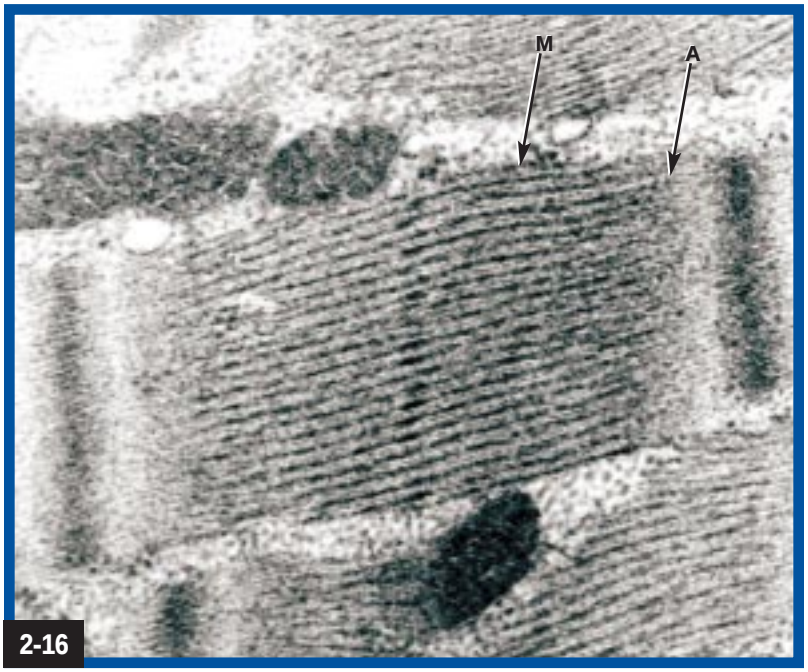
2-14

MICROFILAMENTS The cytoskeleton is composed of many different kinds of protein filaments. The thin lines (arrows) in the cytoplasm of this neuron are actin filaments. *(X530)*



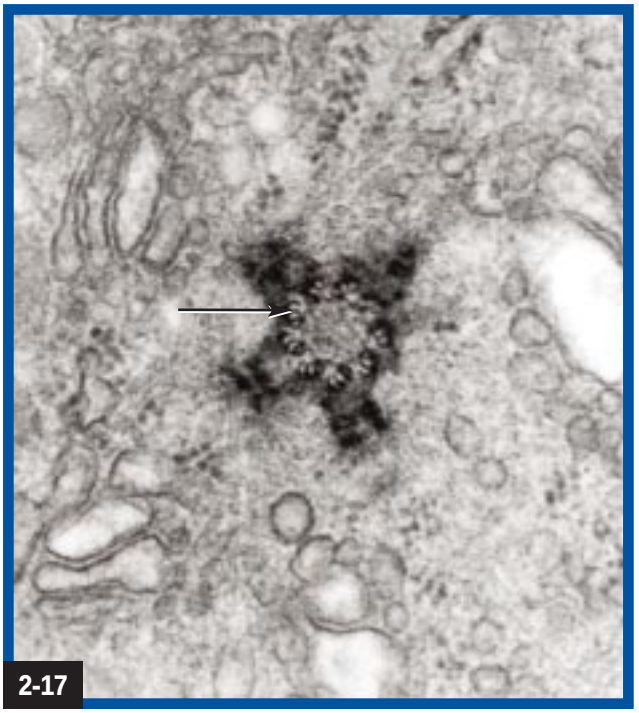
2-15

SKELETAL MUSCLE The banding seen in these skeletal muscle cells is due to the highly organized arrangement of the protein filaments actin and myosin. *(X530)*



2-16

TEM OF ACTIN AND MYOSIN FILAMENTS IN SKELETAL MUSCLE Thick myosin (M) and thin actin (A) filaments are visible in this skeletal muscle cell where they form the contractile apparatus. *(X40,000)* (Courtesy of UCSD Medical Center)



2-17

CENTRIOLES AND THE CENTROSOME Centrioles are paired, cylindrical structures composed of 9 triplets of microtubules. (One triplet is indicated by an arrow.) The centrioles are oriented at 90° to one another and together form the centrosome. The single centriole shown in this transmission electron micrograph is cut in cross section. *(X48,000)*

(Courtesy of UCSD Medical Center)

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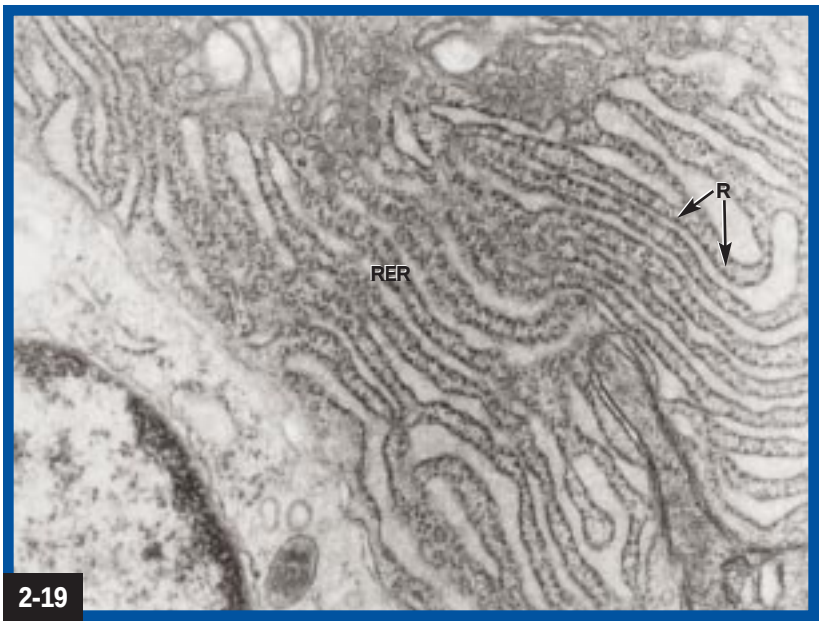
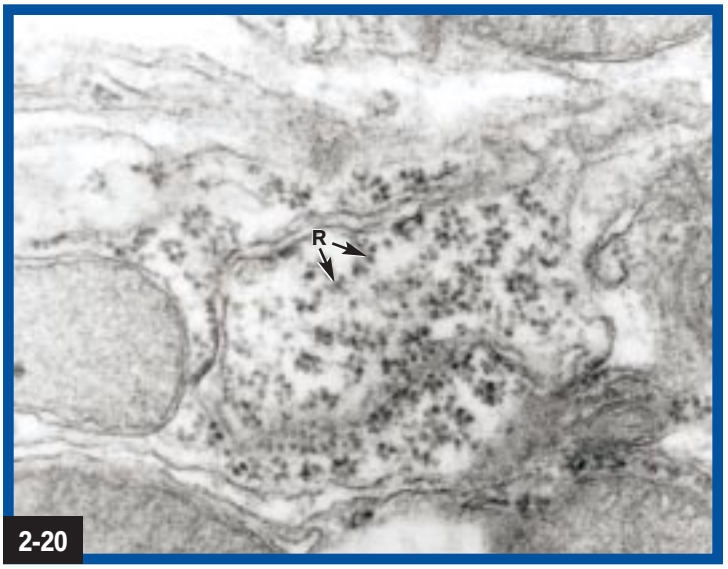
MICROTUBULES OF THE SPINDLE APPARATUS Microtubules (M) are barely visible with the light microscope. Here they are shown forming the spindle apparatus of mitosis. The spindle fibers radiate outward from the centrosome (C) region, which can be localized because of its position at the apex of spindle fibers. *(X530)*



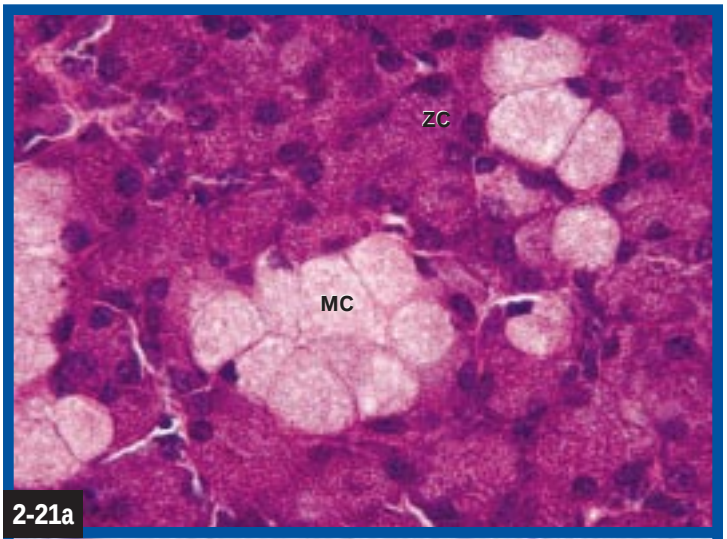
TEM OF RIBOSOMES ON ROUGH ENDOPLASMIC RETICULUM Ribosomes (R) are small, electron dense particles that are the site of protein synthesis. Ribosomes responsible for producing proteins for secretion are bound to the endoplasmic reticulum to form rough endoplasmic reticulum (RER). *(X20,000)*

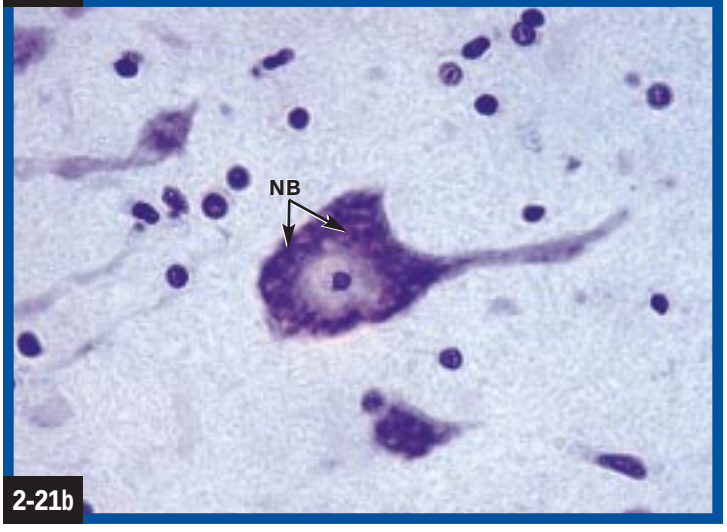
(Courtesy of UCSD Medical Center)



TEM OF FREE RIBOSOMES These free ribosomes (R) are not bound to membrane and produce proteins for internal use. *(X31,500)*

(Courtesy of UCSD Medical Center)





RER AFFECTS THE APPEARANCE OF THE CYTOPLASM The light microscope cannot resolve the detail of RER. However, if it is abundant, the cytoplasm appears granular and dark staining. (a) Zymogenic cells (ZC) produce proteins (enzymes) for secretion. Contrast these with the pale staining mucus cells (MC) visible in the field. Because mucus is rich in polysaccharides, RER is not required in its production. (*X530*) (b) Regions of RER in neurons appear as Nissl bodies (NB) with the light microscope. *(X530)*

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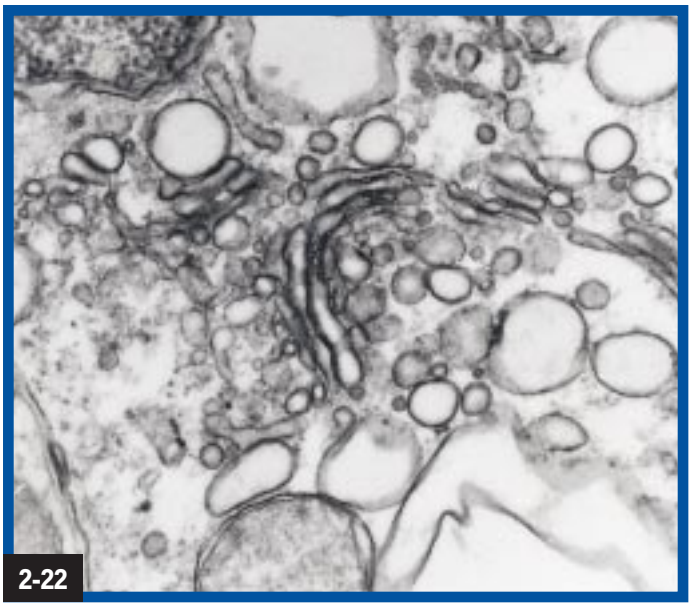
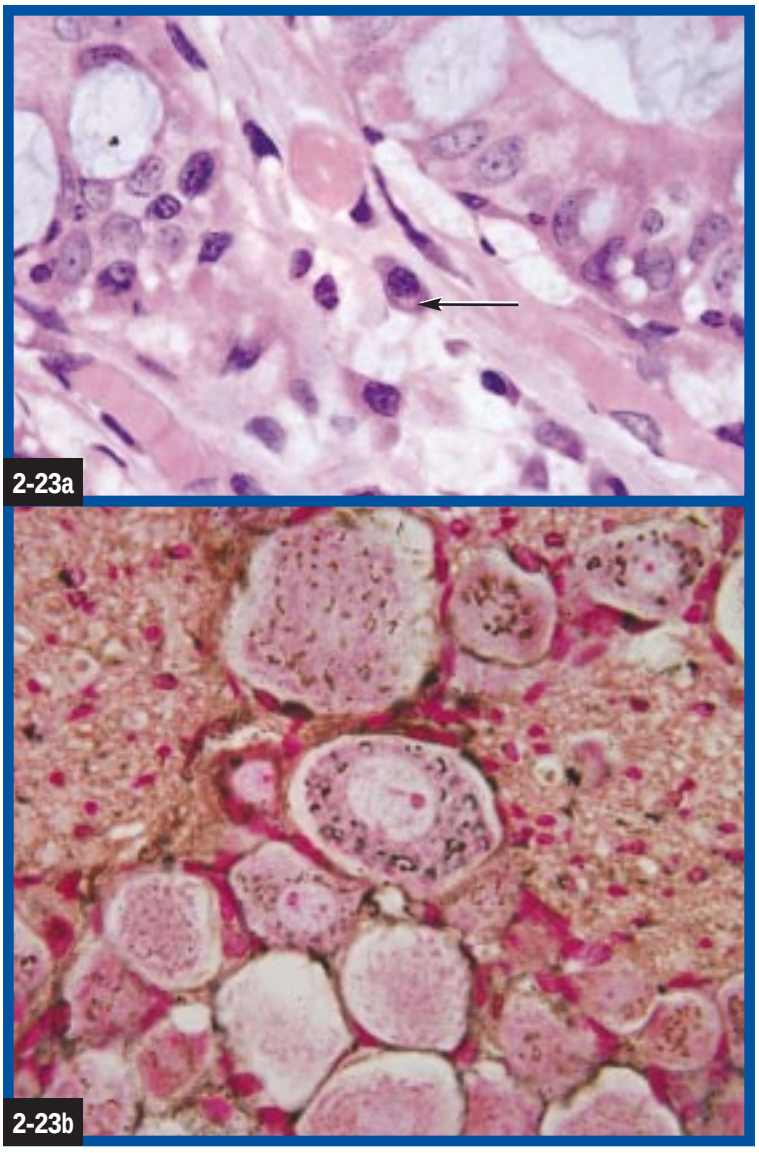
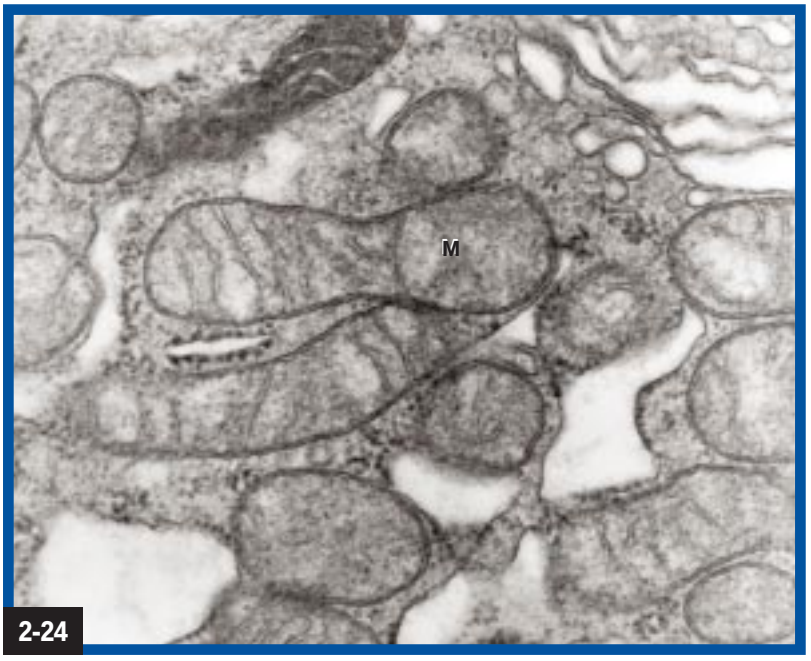


GOLGI APPARATUS AS VIEWED WITH THE TEM This membrane bound organelle is responsible for processing and packaging materials for secretion. *(X24,000)* (Courtesy of UCSD Medical Center)



GOLGI APPARATUS AS VIEWED WITH THE LIGHT MICROSCOPE (a) The Golgi apparatus is occasionally visible as a light staining region near the nucleus of some cells. The cell indicated is an antibody secreting plasma cell. *(X650)* (b) This specimen has been prepared by the DaFano Silver method, a stain that makes Golgi bodies dark. *(X650)*



MITOCHONDRIA Mitochondria (M) are the organelles that house the enzymes and electron transport chain of aerobic respiration. The inner and outer membranes are clearly visible in this TEM. *(X31,500)* (Courtesy of UCSD Medical Center)

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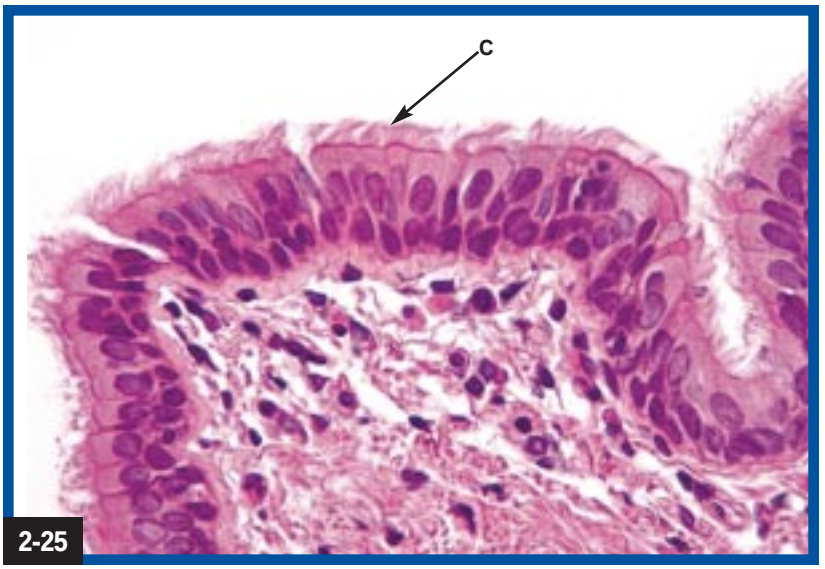
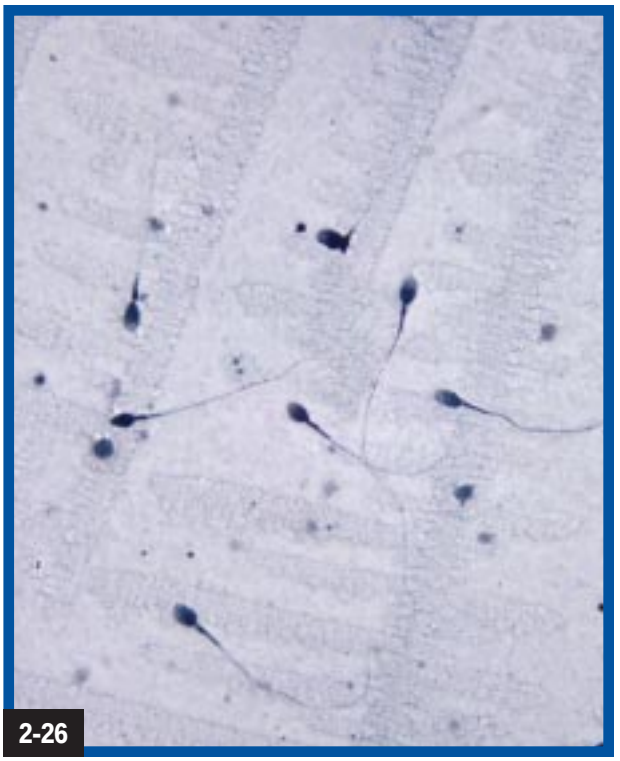


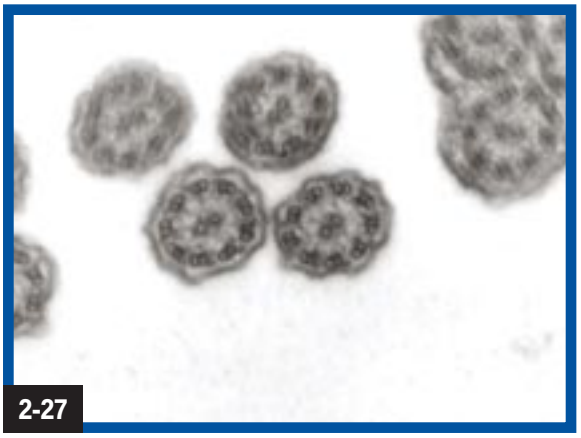
2-25

CILIA Cilia (C) are thin, motile projections responsible for moving materials across the cell's surface. They are more numerous and shorter than flagella. (Compare to Figure 2-26). These cilia are from the respiratory tract where they sweep inhaled materials away from the lungs. Do not confuse cilia with a brush border of microvilli. Microvilli are usually shorter and individual ones cannot be seen, as is often the case with cilia. *(X530)*



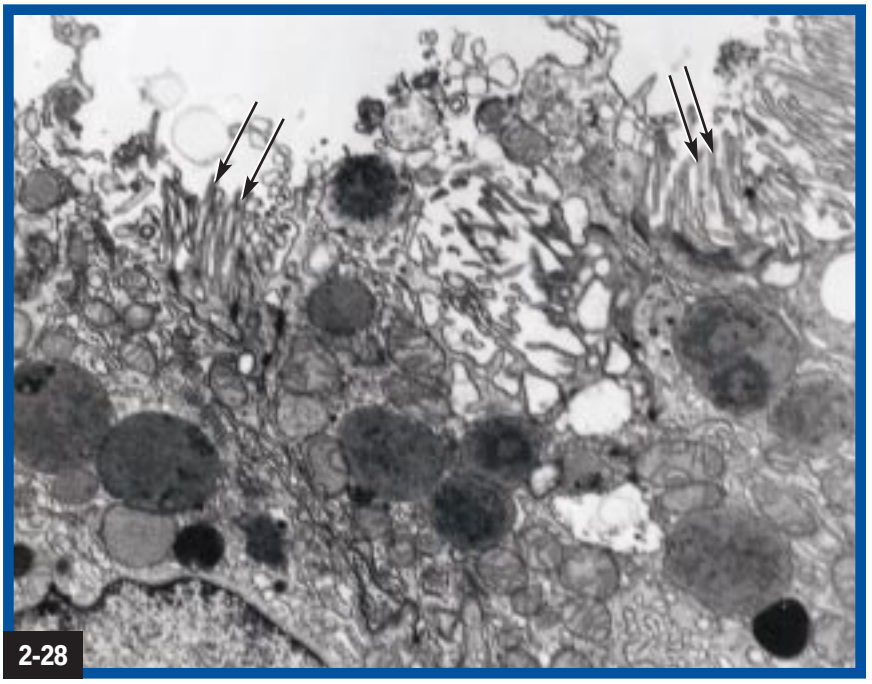
2-26

FLAGELLA Sperm are the only human cells that have flagella. The tails of these sperm cells are the flagella. *(X650)*



2-27

CROSS SECTION OF CILIA The 9+2 microtubular arrangement is apparent in this TEM of cilia in cross section. Flagella have exactly the same arrangement. *(X40,000)* (Courtesy of UCSD Medical Center)



2-28

MICROVILLI Microvilli (arrows) are foldings of the surface membrane that increase surface area for absorption. *(X15,000)* (Courtesy of UCSD Medical Center)

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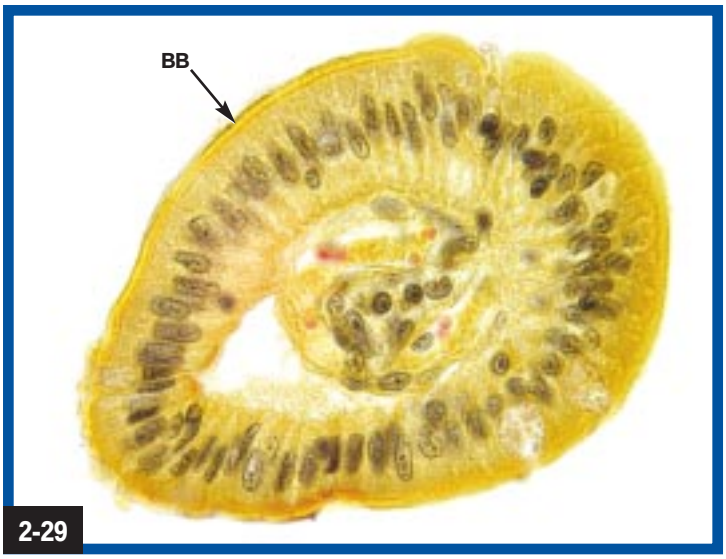
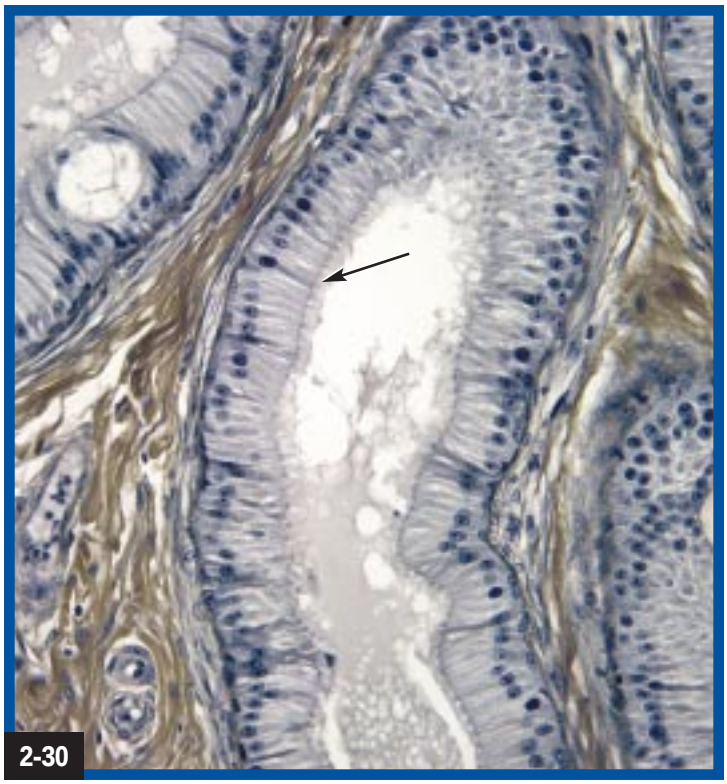
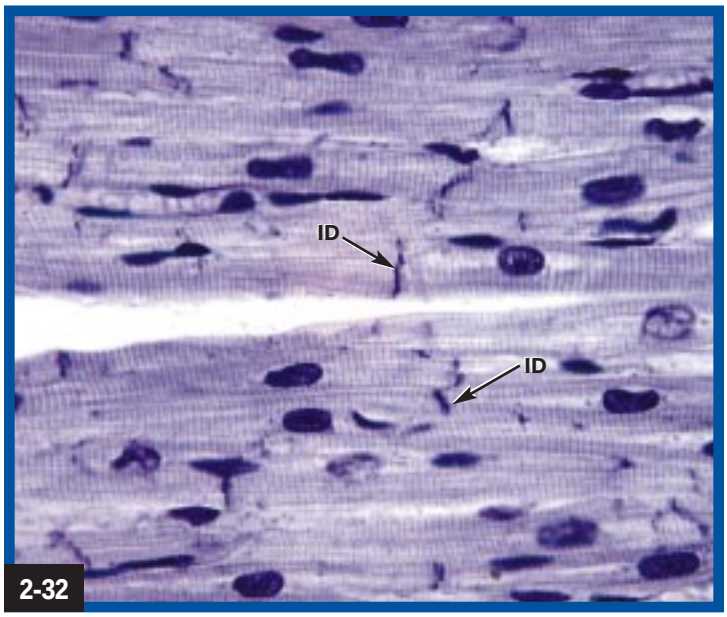


BRUSH BORDER Individual microvilli are not visible with the light microscope. Rather, a fuzzy band—the brush border (BB)—is seen. These cells are from the small intestine. Do not confuse a brush border with cilia. Typically, individual cilia can be discerned, and often they are clumped, like bent teeth on a comb. *(X530)*



STEREOCILIA The misnamed stereocilia are actually long microvilli. These are from the epididymis. *(X240)*

TERMINAL BARS The junctions between adjacent intestinal epithelial cells are sometimes seen as terminal bars. Use of the electron microscope has uncovered several different types of intercellular junctions. Also note the brush border (BB). *(X530)*



INTERCALATED DISCS The junctions between adjacent cardiac muscle cells are complex and include highly interdigitated cell surfaces joined by several types of intercellular attachments. In the light microscope, these appear as the intercalated discs (ID). Do not confuse intercalated discs with the striated pattern produced by the organized arrangement of actin and myosin filaments. *(X530)*

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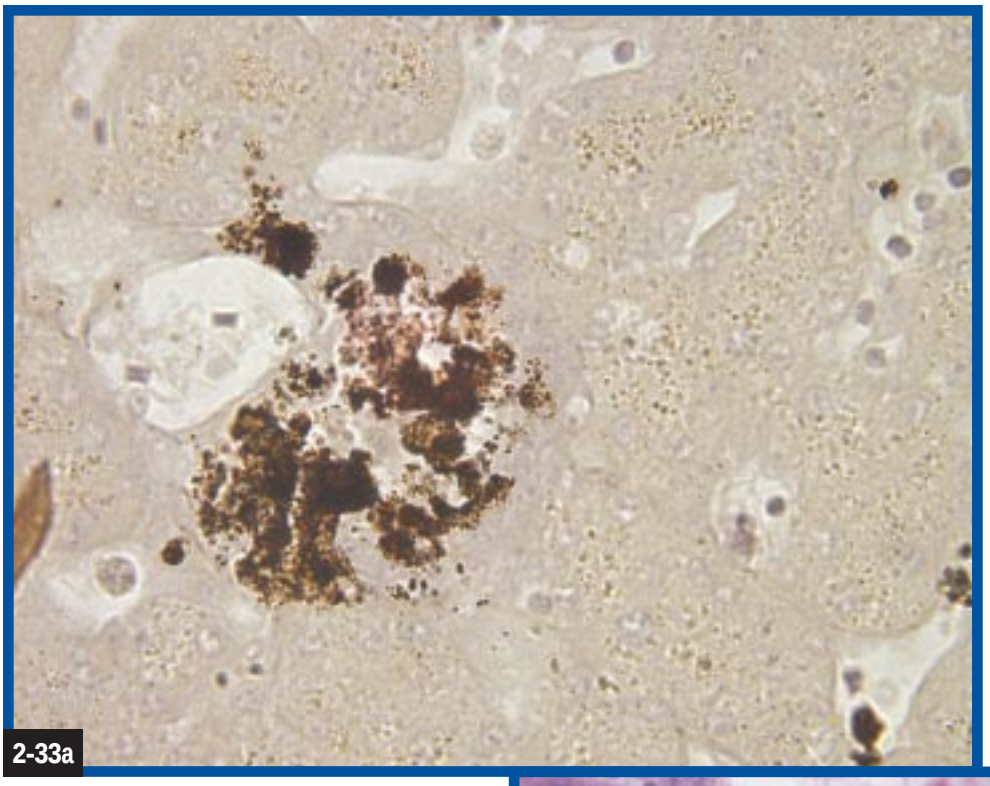
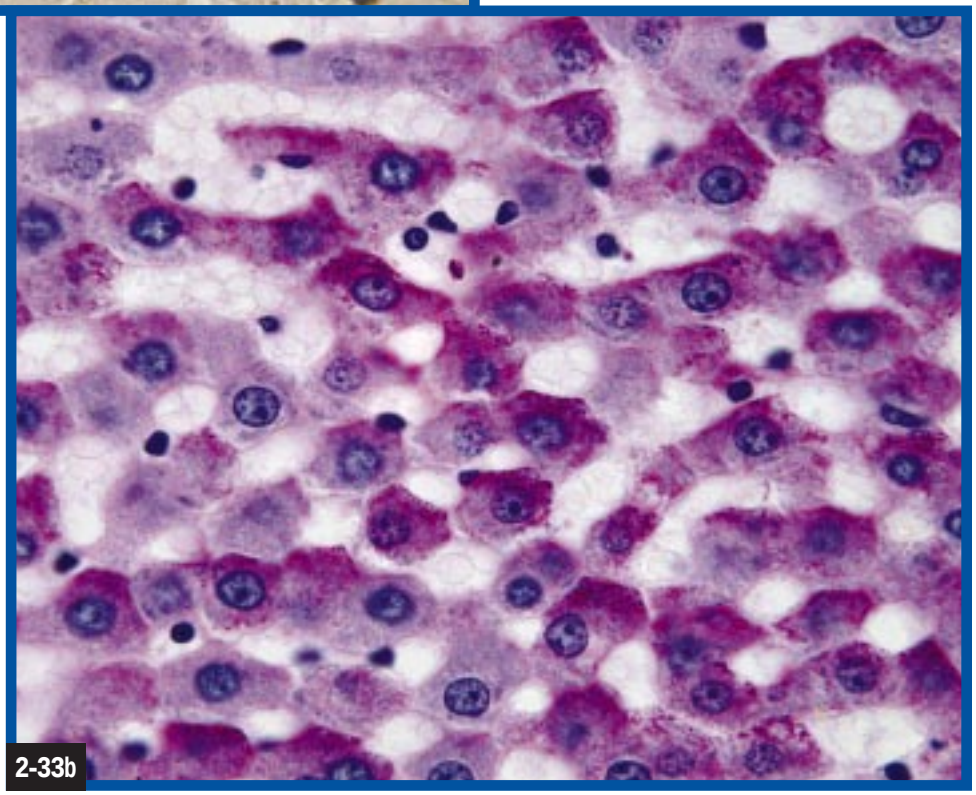


2-33a

CELLULAR INCLUSIONS Some storage products, such as glycogen and lipid, appear in the cytoplasm of cells. (a) This liver specimen has been stained for lipids with osmium tetroxide, which makes them appear brownish. (*X650*) (b) PAS positive glycogen in this liver specimen appears reddish. *(X650)*



2-33b

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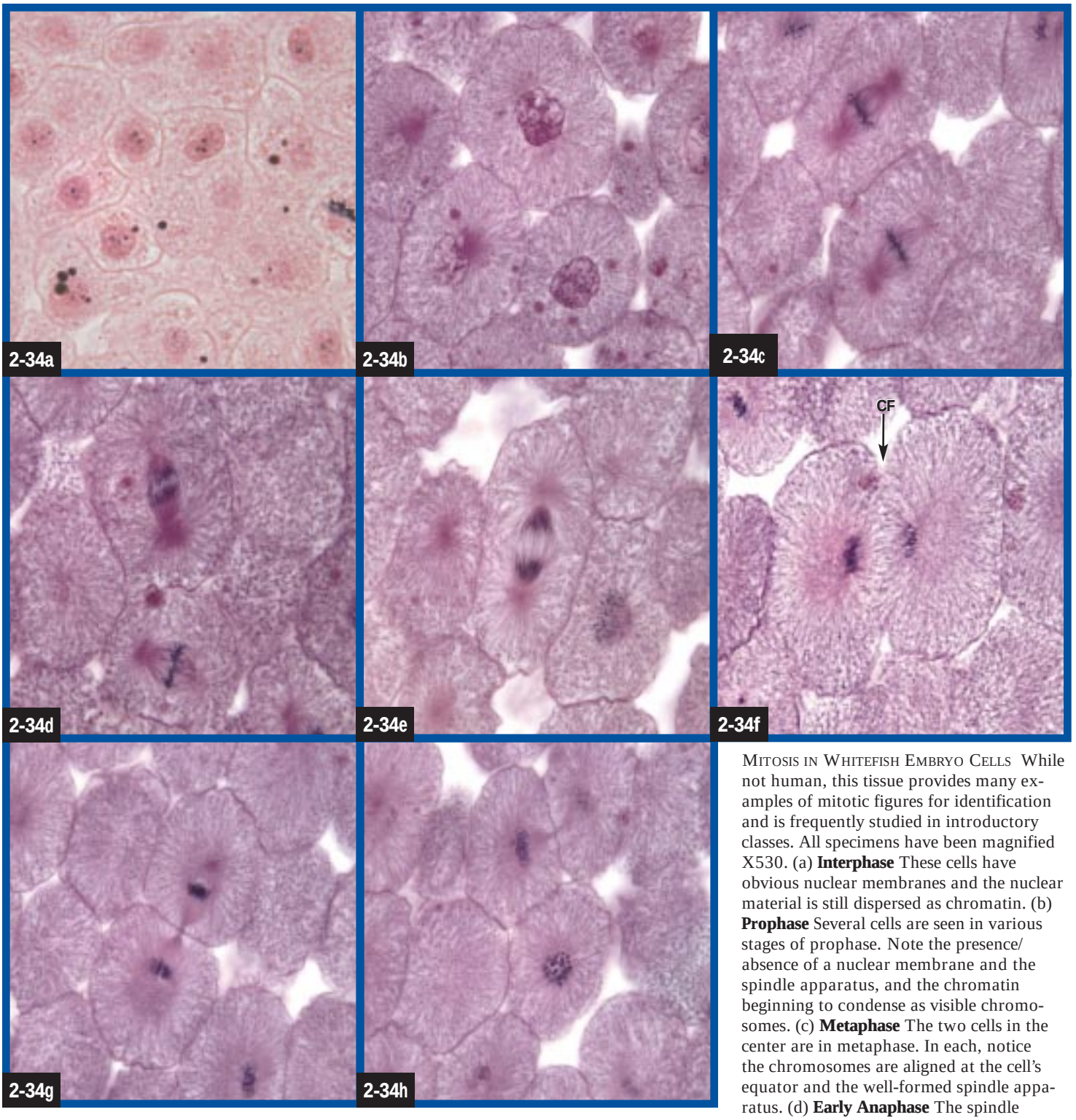

MITOSIS IN WHITEFISH EMBRYO CELLS While not human, this tissue provides many examples of mitotic figures for identification and is frequently studied in introductory classes. All specimens have been magnified X530. (a) **Interphase** These cells have obvious nuclear membranes and the nuclear material is still dispersed as chromatin. (b) **Prophase** Several cells are seen in various stages of prophase. Note the presence/absence of a nuclear membrane and the spindle apparatus, and the chromatin beginning to condense as visible chromosomes. (c) **Metaphase** The two cells in the center are in metaphase. In each, notice the chromosomes are aligned at the cell's equator and the well-formed spindle apparatus. (d) **Early Anaphase** The spindle apparatus has begun to separate the chromosomes in the upper cell. The cell near the bottom of the field is in metaphase. (e) **Late Anaphase** The chromosomes are close to the centrosomes, which means they have moved apart just about as far as they will go. (f) **Telophase** The chromosomes have reached opposite poles of the cell and the spindle fibers have begun to break down. The cleavage furrow (CF) has also begun to form. (g) **Late Telophase and Cytokinesis** The cleavage furrow has nearly divided the two cells, so cytokinesis is almost complete. Telophase will continue with the chromosomes dispersing as chromatin and the nuclear envelope reforming. (h) **Polar View** The cell in the center doesn't fit any of the descriptions because it is being viewed from one end (pole) rather than from above.

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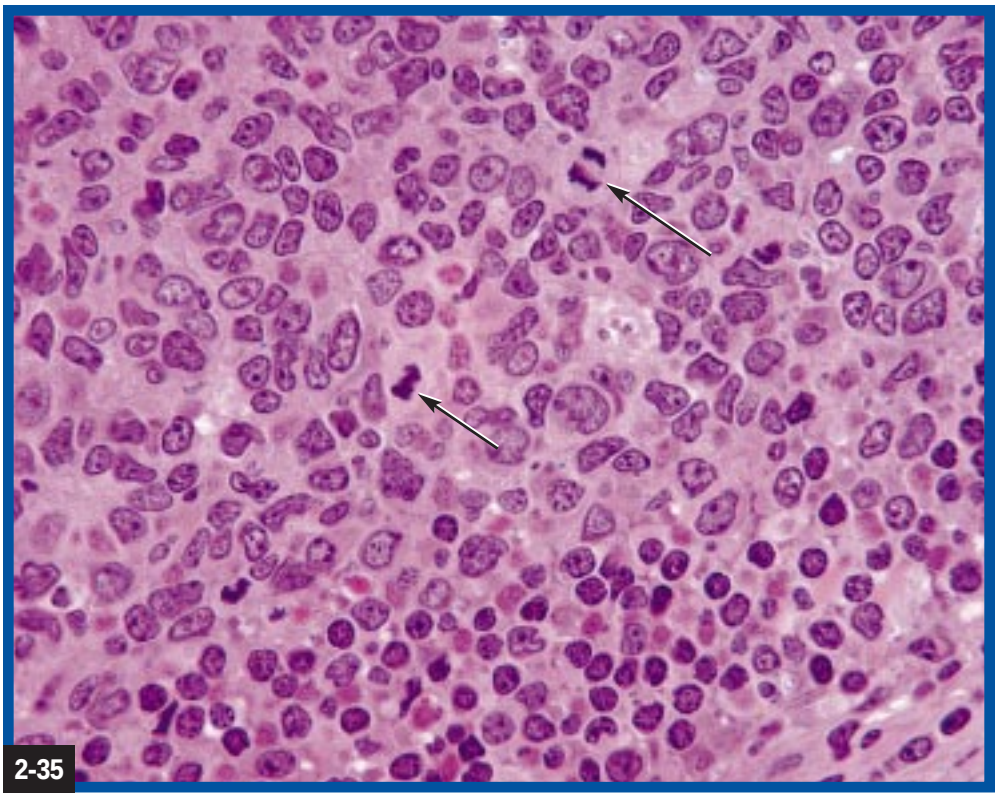

2-35

MITOSIS IN LYMPHATIC TISSUE
Mitotic figures can also be seen by careful observers in many different tissues. This specimen is from a lymph node. Several cells are undergoing mitosis (arrows), but most are in interphase. Notice the chromatin granules and the nucleoli in these nondividing cells. *(X650)*

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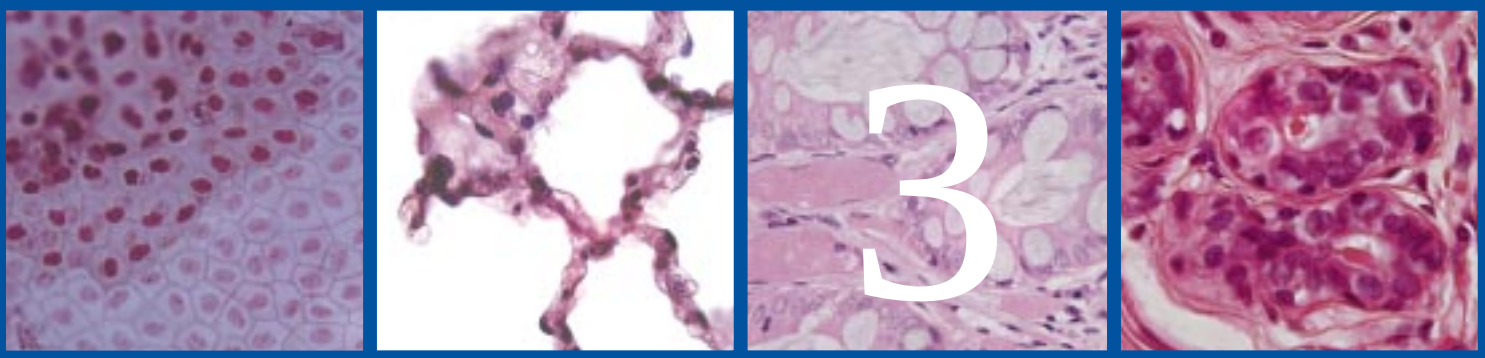
Epithelial Tissue

CHAPTER 3



Basic Characteristics of Epithelial Tissues

Epithelial tissues or **epithelia** cover most surfaces in the body. Typically, the cells are joined by junctional complexes (see Chapter 2) into sheets with little intercellular material (Figure 3-1). (For a graphic example, recall the last time you peeled after a sunburn!) Epithelia rest on a **basement membrane** that separates them from the underlying connective tissue (Figure 3-2). Electron micrographs show that the basement membrane is composed of a **basal lamina** (derived from the epithelial cells) and a **lamina reticularis** (produced by fibroblast cells of the connective tissue). Blood vessels do not penetrate the basement membrane, making epithelia *avascular*.

Epithelial Membranes

Since epithelia are avascular, they rely on nourishment from the capillaries of the underlying connective tissues. This results in a structural and functional association between an epithelium and its underlying connective tissue: an **epithelial membrane**. Epithelial membranes are of three types. **Mucous membranes** line surfaces open to the external environment and often secrete mucus (Figure 3-3). Examples are the membranes lining the digestive, respiratory, urinary and reproductive tracts. **Serous membranes** line the ventral body cavities—pericardial, pleural, and peritoneal cavities—as **pericardium**, **pleura**, and **peritoneum**, respectively. The epithelial component of serous membranes is called **mesothelium**. **Cutaneous membrane** is the skin.

Functions of Epithelia

The structures of epithelia vary depending on their functions. Some functions of epithelia are:

- Mechanical protection from abrasive forces (*e.g.*, the epidermis).
- Absorption of substances from the **lumen** (inner portion) of a tubular organ (*e.g.*, intestinal epithelium). The luminal surface is usually modified with **microvilli** to increase the surface area and improve efficiency of absorption.
- Secretion of materials (*e.g.*, intestinal epithelium). This epithelium often has single-celled, mucigen-secreting **goblet cells** (see page 24) in it.
- Lubrication of surfaces (*e.g.*, mesothelium of pericardium).
- Formation of a diffusion membrane (*e.g.*, alveoli of lung).

Epithelial Terminology

Some important terminology associated with epithelia is illustrated in Figure 3-4. If the cell is actually on the surface (and is not buried in the epithelium) the surface edge of the cell is called the **free**, **apical**, or **luminal edge**. The sides contacting other epithelial cells are called **lateral edges**, and the edge in contact with the basement membrane is called the **basal edge**. If the epithelium consists of more than one layer, the **basal cells** are closest to the basement membrane.

Epithelia are named based on two main criteria: the number of cell layers and the shape of the cells at the

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surface. **Simple epithelia** have a single layer of cells, so all cells contact the basement membrane. **Stratified epithelia** are made of two or more cell layers and only the basal cells contact the basement membrane. **Squamous cells** are flat with flattened nuclei. (Note: The shape of the nucleus is important in identifying an epithelium because nuclei tend to be the most obvious part of a cell.) **Cuboidal cells** are cube-shaped with spherical nuclei positioned in the cell's center. **Columnar cells** are taller than wide and have an elongated, basal nucleus. To completely name an epithelium, both the number of cell layers and the shape of cells at the surface must be included.

Simple Epithelia

Simple squamous epithelium is composed of a single layer of flat cells. It forms the alveoli of the lungs (Figure 3-5) where it participates in forming the respiratory membrane through which gases diffuse, and glomerular capsules of the kidney where blood filtration occurs (Figure 3-6). The simple squamous lining of blood vessels and the heart is called **endothelium** (Figure 3-7). **Mesothelium** is the epithelial component of serous membranes and secretes a lubricating fluid (Figures 3-1 and 3-8).

Simple cuboidal epithelium is composed of a single layer of cube-shaped cells. It is found in kidney tubules (Figure 3-9) where it is involved in secretion and absorption, and ducts of glands (Figure 3-10), among other places.

Simple columnar epithelium (Figure 3-11) is made of a single layer of tall cells with basally positioned, elongated nuclei. It is typically involved in absorption and secretion, and often has microvilli and goblet cells (Figure 3-12).

Stratified Epithelia

Stratified squamous epithelium is composed of several to many layers of cells with the superficial layers being flattened. Since it is so thick, it is generally found in places subjected to abrasion. **Keratinized stratified squamous** (Figures 3-13 through 3-16) is found on dry surfaces (*e.g.*, the skin). As the epithelial cells produced at the base get pushed to the surface, they die and undergo changes, including accumulation of the protein keratin. The dead cells so-formed provide a waterproof, microbe-proof, abrasion barrier.

Nonkeratinized stratified squamous (Figure 3-17) is found in moist areas of the body not subjected to as much abrasion (*e.g.*, oral cavity, esophagus, and vagina). Unlike the keratinized variety, the surface cells are living and have normal nuclei.

Stratified cuboidal and **stratified columnar epithelia** generally consist of only a couple of layers. They are found in the ducts of some glands (Figures 3-18 and 3-19), with the cell height corresponding to the duct's size.

Other Epithelia

Some epithelia do not conform very well to the conventional naming criteria. These are considered in this section.

Transitional epithelium, found lining the urinary bladder and ureters, is stratified and specialized for stretching. When in the stretched state (Figure 3-20), all cell layers are flattened. When relaxed (Figures 3-21 and 3-22), the cells take on an irregular appearance, especially in the most superficial layer where they often bulge into the lumen, giving the surface a scalloped appearance.

Pseudostratified ciliated columnar epithelium—which is shortened to **PSCC**—is not a truly stratified epithelium since all cells are in contact with the basement membrane (Figures 3-2, 3-23, and 3-24). However, not all cells reach the surface; some cells are short, some are tall, and others are intermediate in height. This variation in cell height results in nuclei being seen at different levels in the epithelium, giving the false impression of stratification—hence "*pseudo*stratified." And, since the cells that reach the surface are taller than wide, the epithelium is considered to be columnar. It is most associated with the respiratory tract where it lines the nasal cavity, trachea, and bronchi. Goblet cells produce mucus that traps dust and other particles in inspired air, then the cilia sweep the mucus toward the pharynx where it is swallowed.

Glandular Epithelia

Glandular epithelia are specialized for secreting materials. They develop from typical lining epithelium that grows down (*invaginates*) into deeper tissues and as such is not found on the surface. **Exocrine glands** remain connected to the surface and deliver their secretion to it by way of a duct. They are the subjects of this section. **Endocrine glands** (Chapter 10) lose the connection to the surface during development, so the secretion is transported by the blood.

Unicellular glands are represented by the abundant **goblet cells** of the respiratory and digestive tracts (Figures 3-25 and 3-26). Goblet cells secrete **mucigen**, which converts to mucin when hydrated. Mucin is a major component of **mucus**.

Multicellular exocrine glands are more complex, with specialized duct cells and secretory cells (Figure 3-27). Photomicrographic examples are provided in Figures 3-28 through 3-34. Multicellular glands are classified according to their duct(s) and their secretory portions. If the duct is unbranched, the gland is **simple**; if it branches, the gland is **compound**. If the secretory portion is about the same size as the duct, the gland is **tubular**. If the secretory cells are larger than the duct, it is an **acinar** (or **alveolar**) **gland**. Some glands have both acinar and tubular secretory portions.

The secreting cells and the ducts comprise the **parenchyma** of the gland. In addition, there may be a connective

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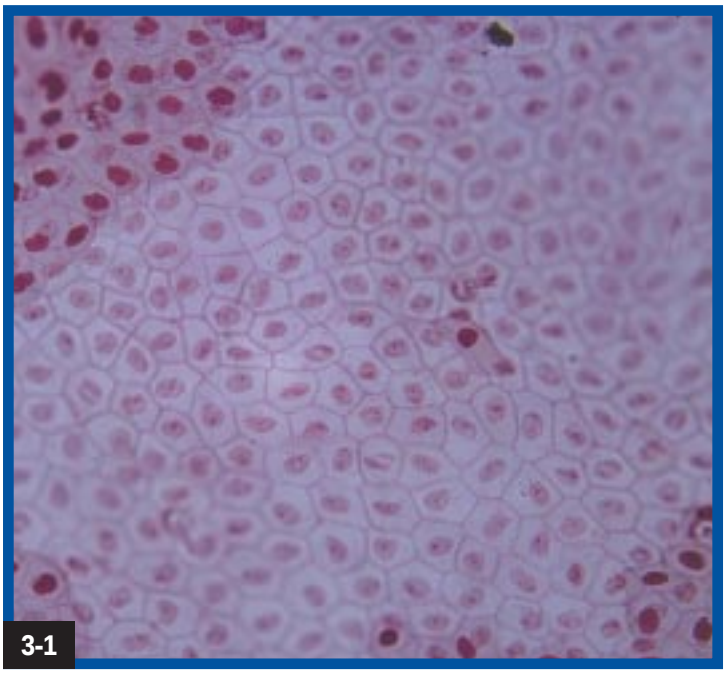
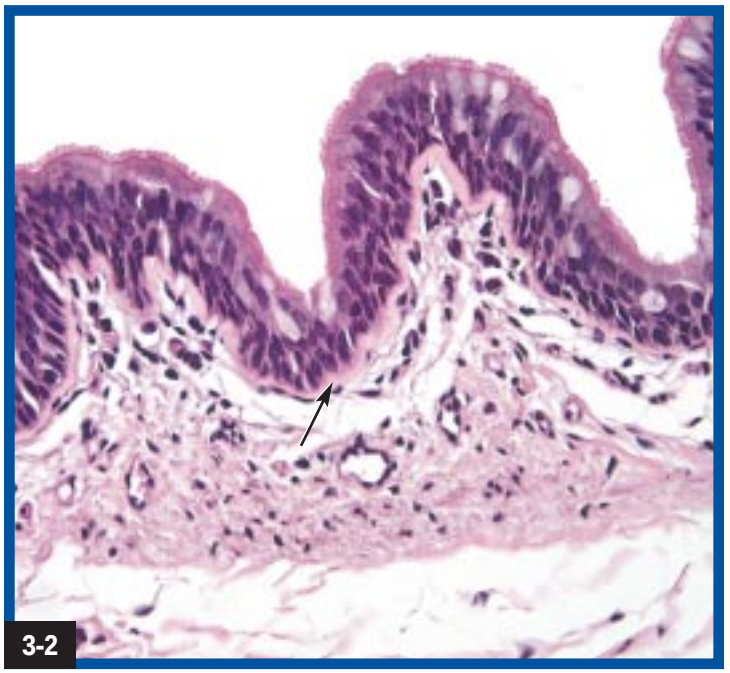
tissue stroma in the gland that supports the parenchyma. In larger glands, the connective tissue **capsule** on the surface sends branches into the gland and divides it into **lobes** and **lobules**.

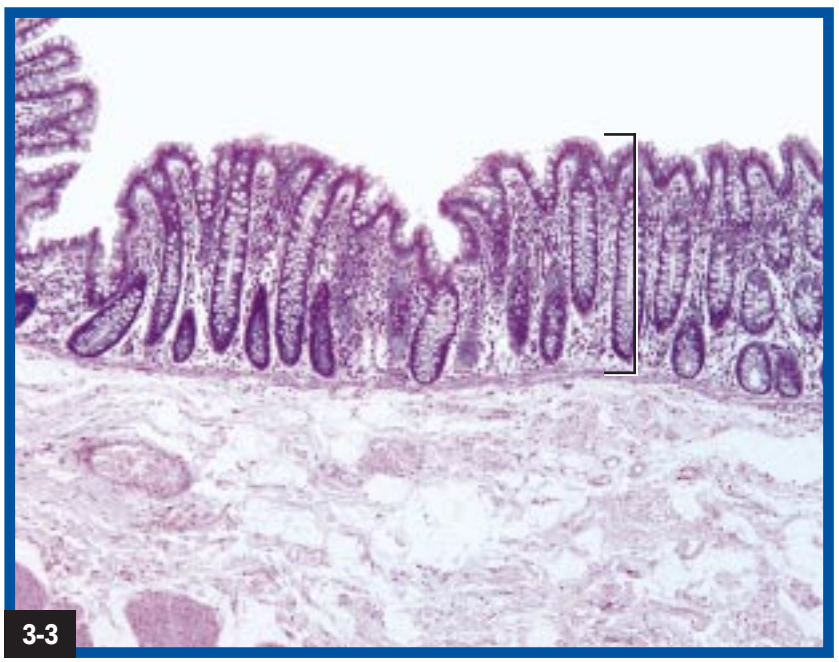
Myoepithelial cells (Figure 3-35) are associated with some acini. These are contractile epithelial cells that push the gland's secretion into the duct. They are found in salivary and sweat glands.



EPITHELIUM IS A CELLULAR TISSUE This is a whole mount of mesothelium, an epithelium composed of a single layer of flat cells. Viewed from the surface, the very cellular and sheet-like nature of epithelial tissue is apparent. Most specimens you will encounter are viewed in section, so are seen from the side. *(X300)*



LIGHT MICROGRAPH OF A BASEMENT MEMBRANE Shown is an epithelium from the respiratory tract that has a prominent basement membrane (arrow). In sections of most epithelia, the basement membrane is not as obvious. In many cases, all that is visible is the junction between the epithelium and the underlying connective tissue. *(X240)*



AN EPITHELIAL MEMBRANE All epithelial membranes (mucous, serous, and cutaneous membranes) are composed of an epithelium and its underlying connective tissue. In each, the avascular epithelium relies on the capillaries of the connective tissue for its oxygen and nutrients, and thus forms a functional as well as a structural unit. Illustrated here is the colon's mucous membrane. Notice the numerous, pale staining mucus cells in the epithelium. *(X70)*

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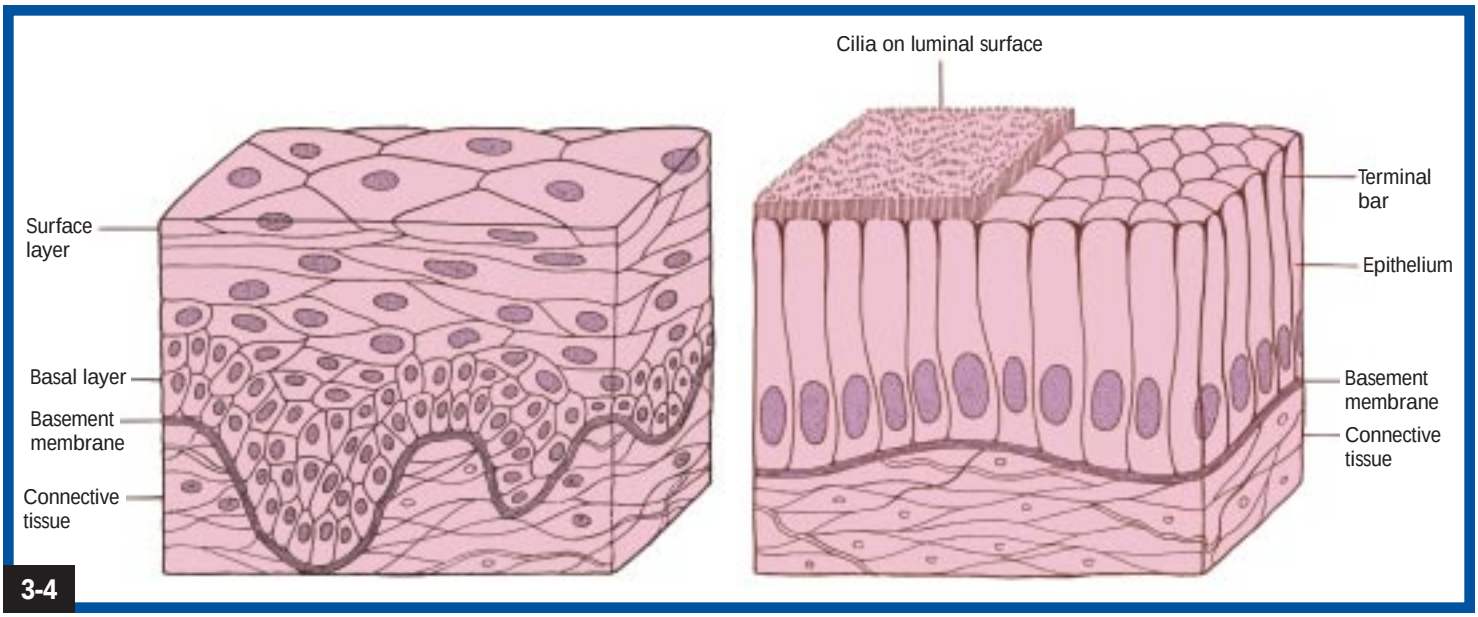
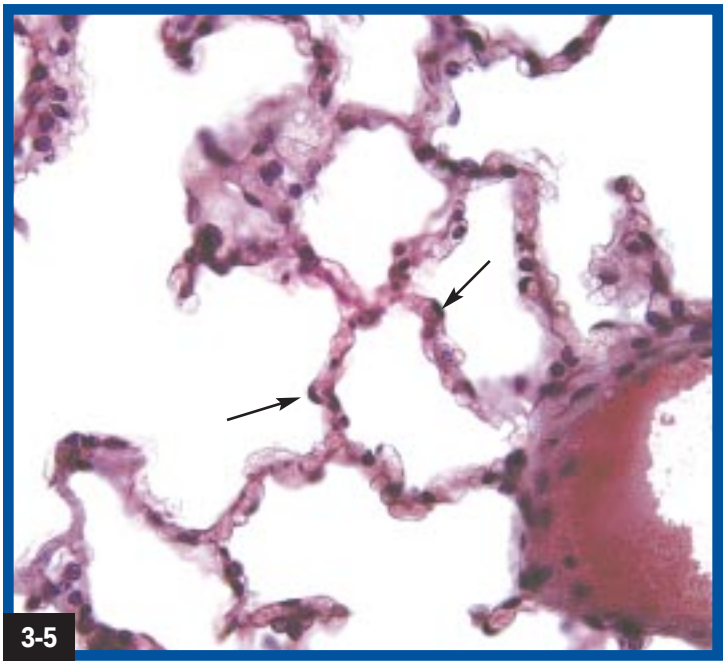
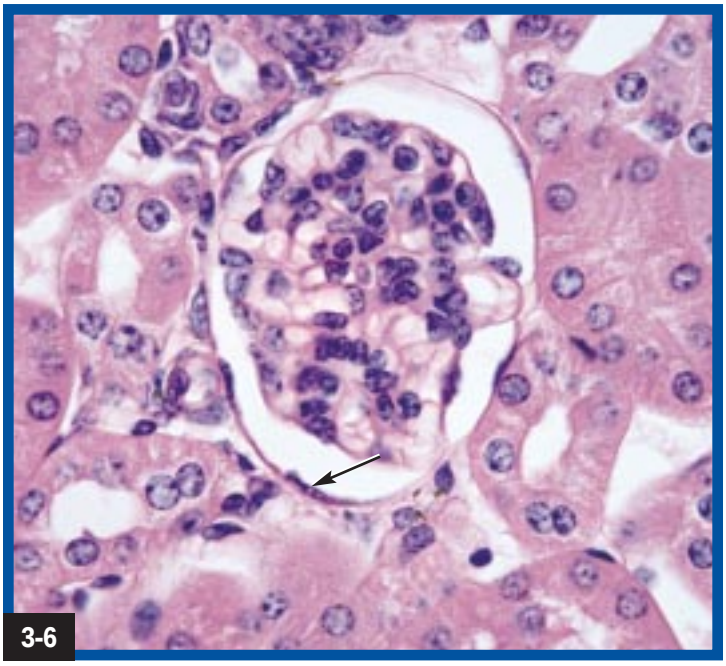


EPITHELIAL TERMINOLOGY Illustrated are standard descriptive terms associated with epithelia. Notice the importance of the basement membrane and surface as points of reference.



SIMPLE SQUAMOUS EPITHELIUM OF THE LUNG Notice that the squamous cells are so thin, only their nuclei are visible (arrows). *(X380)*



SIMPLE SQUAMOUS EPITHELIUM OF THE KIDNEY The renal corpuscles of the kidney are lined with a simple squamous epithelium (arrow). Again, the flattened nuclei are the most prominent feature of the epithelium. *(X530)*

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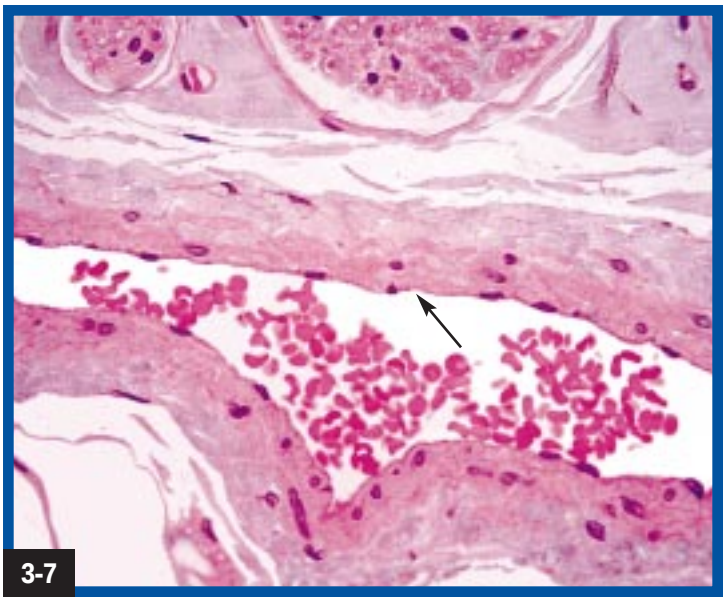
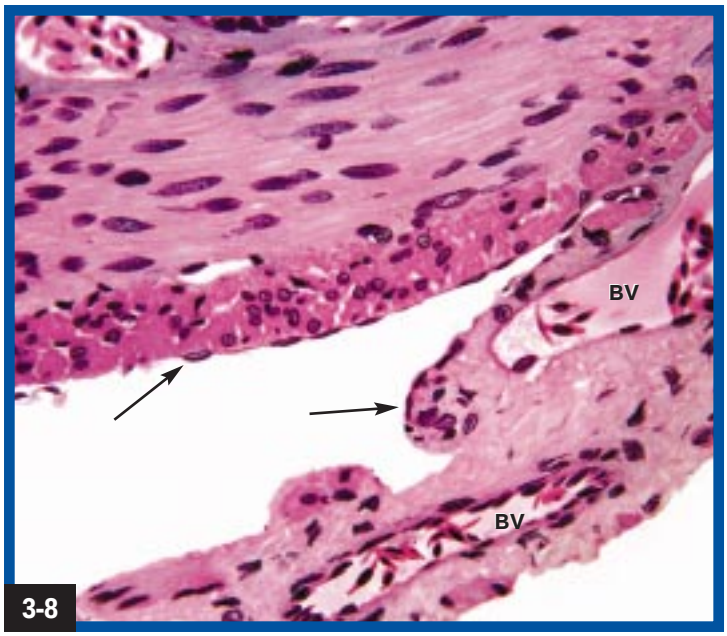
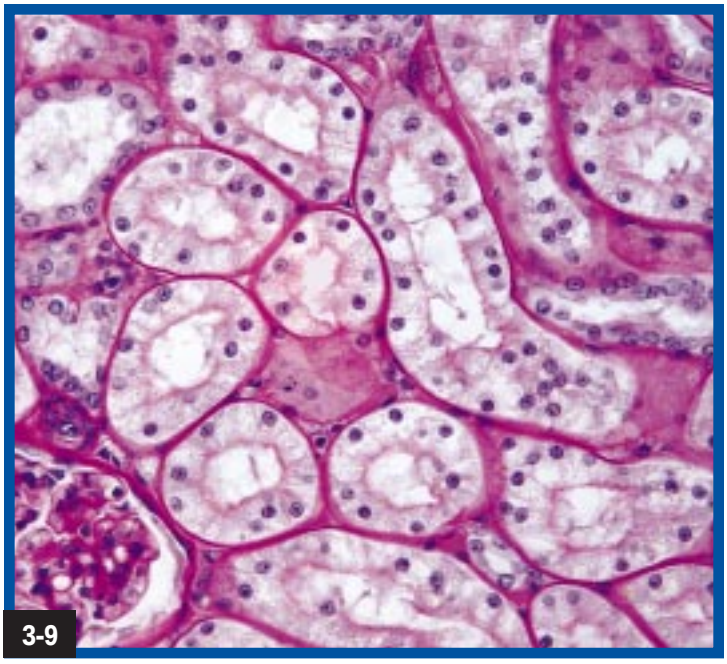


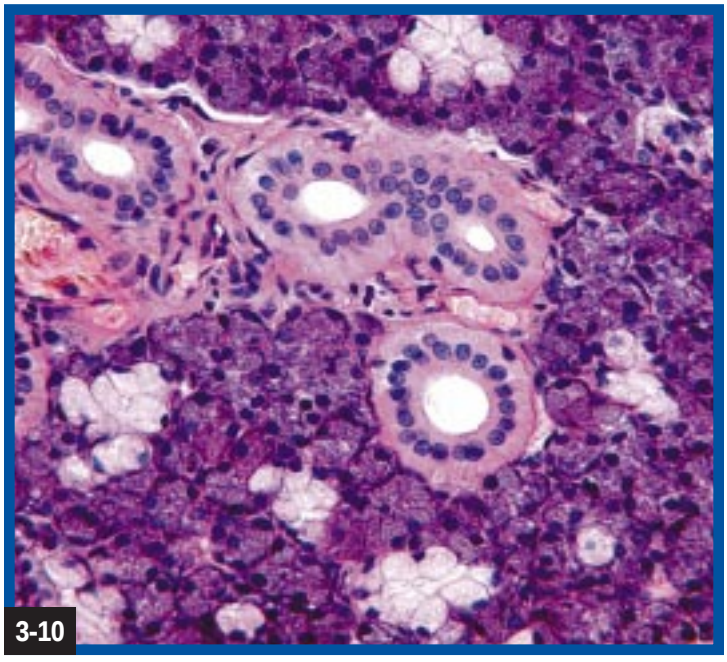
SIMPLE SQUAMOUS ENDOTHELIUM The inside of all blood vessels and the heart are lined with a simple squamous endothelium (arrow). This micrograph is of a small vein. *(X320)*



MESOTHELIUM The outer surface of organs in the ventral body cavity is lined with a serous membrane made of a connective tissue and a simple squamous mesothelium (arrows). Also note the simple squamous endothelium lining the various blood vessels (BV). *(X150)*



SIMPLE CUBOIDAL EPITHELIUM These renal tubules are lined with a simple cuboidal epithelium. The lateral membranes are not visible between all cells, but their cuboidal shape is still obvious. The cells apparently missing nuclei are the result of their nuclei not being in the plane of the section. The pinkish line at the base of the epithelium is the basement membrane, prominently stained by the PAS method. *(X320)*



A TALL SIMPLE CUBOIDAL EPITHELIUM The pink cells are considered simple cuboidal epithelium rather than simple columnar because of the shape and position of their nuclei. In some cases, classification between cuboidal and columnar becomes a judgment call. These are ducts in a salivary gland. *(X320)*

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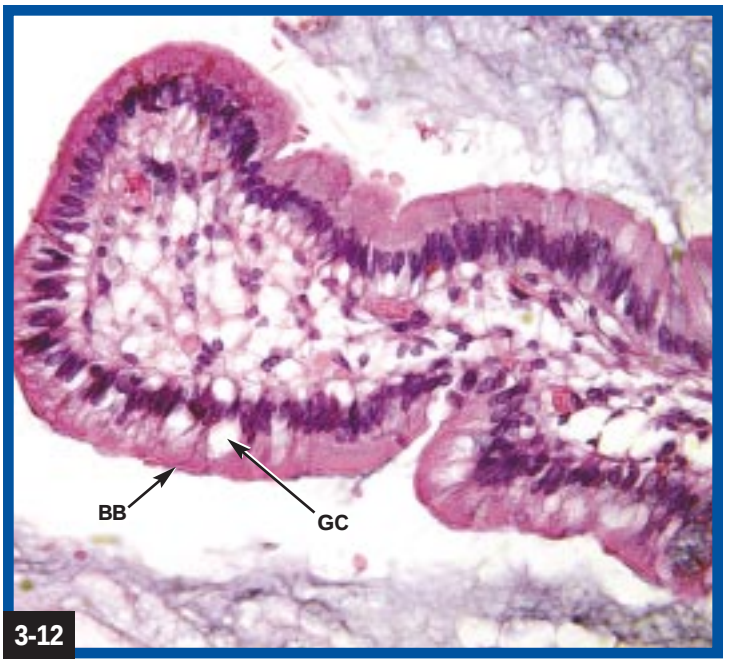
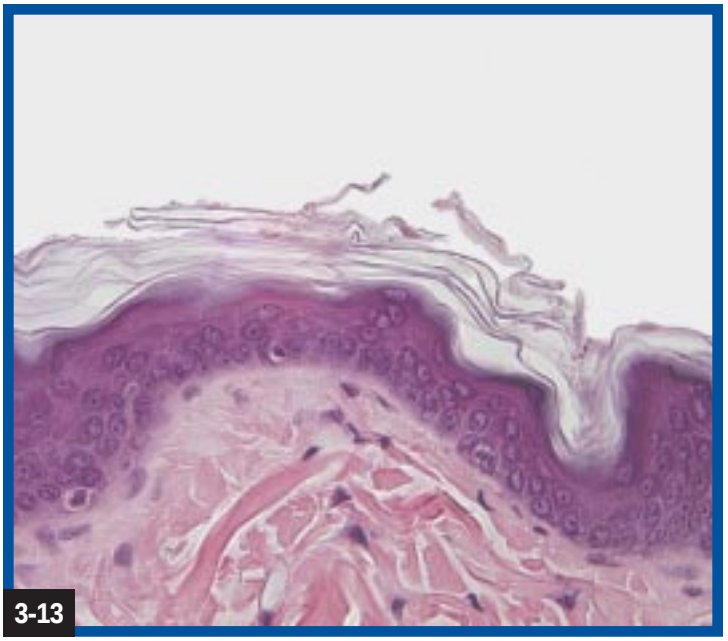
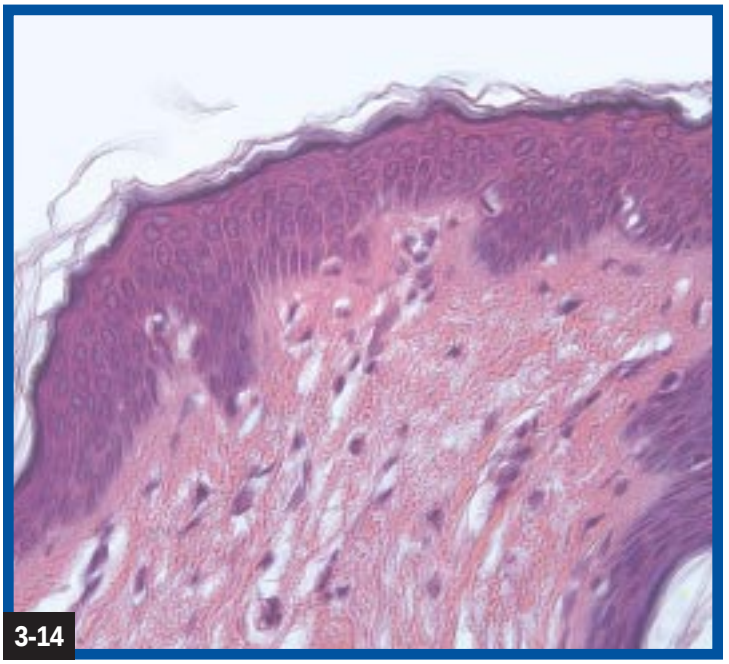
SIMPLE COLUMNAR FROM THE STOMACH These simple columnar cells are characterized by a tall shape and a basal, elongated nucleus. The basement membrane is not apparent in this specimen, but it is still clear where the epithelium ends and the connective tissue begins (arrow). The region indicated by the bracket is a curved surface lined by the same epithelium, but cut tangentially. Notice the similarity of the light region to the luminal portion of the other cells. *(X320)*



SIMPLE COLUMNAR EPITHELIUM WITH GOBLET CELLS AND A BRUSH BORDER This intestinal epithelium is simple columnar. The large pale staining cells are goblet cells (GC) that secrete mucus. A brush border (BB) is clearly visible over most of the surface. *(X320)*



THIN KERATINIZED STRATIFIED SQUAMOUS EPITHELIUM The flat surface cells are dead and form the shredded keratinized layer. This specimen is from abdominal skin. The whole epithelium is only a few cells thick. *(X320)*



MORE THIN KERATINIZED STRATIFIED SQUAMOUS EPITHELIUM This specimen illustrates the convention that epithelia are named according to the cell shape *at the surface*. Note how tall the basal cells are. *(X320)*

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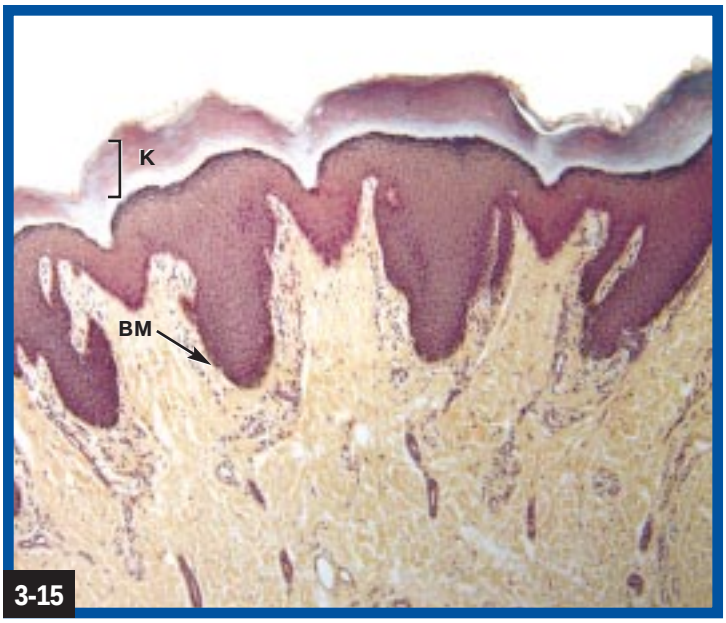
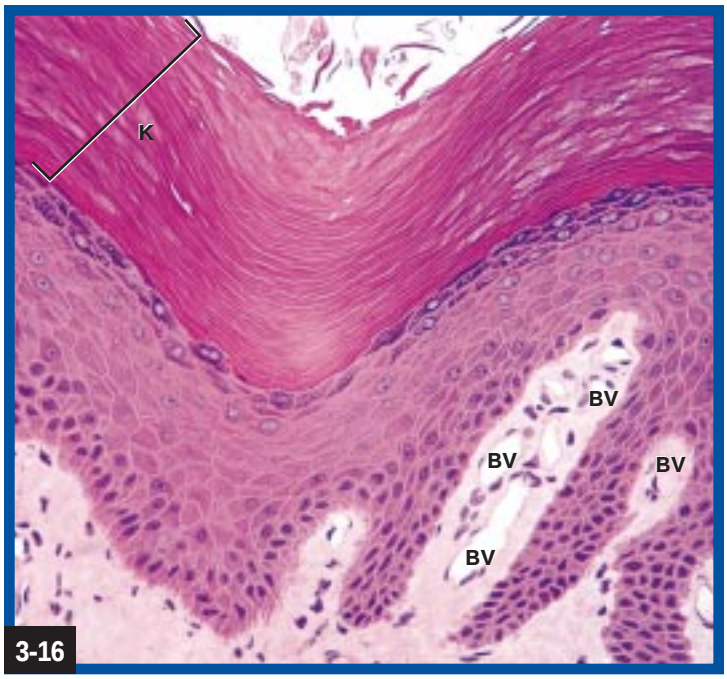
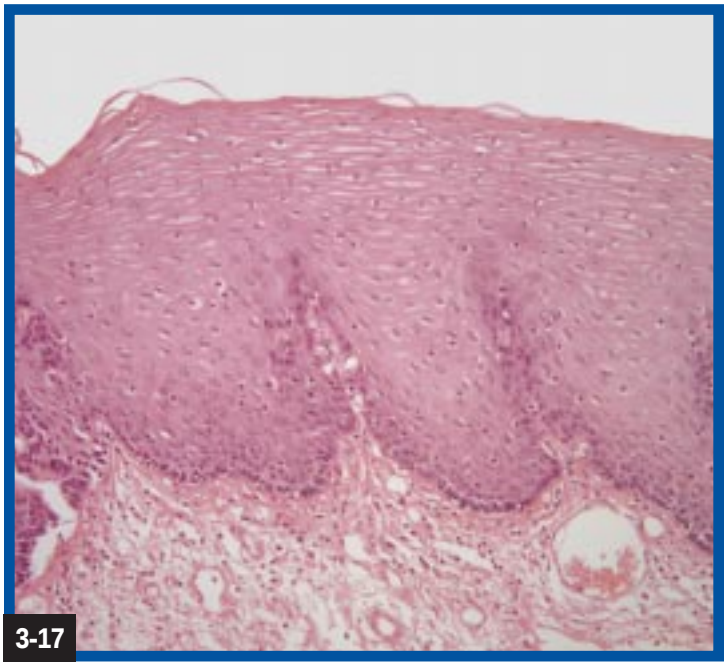


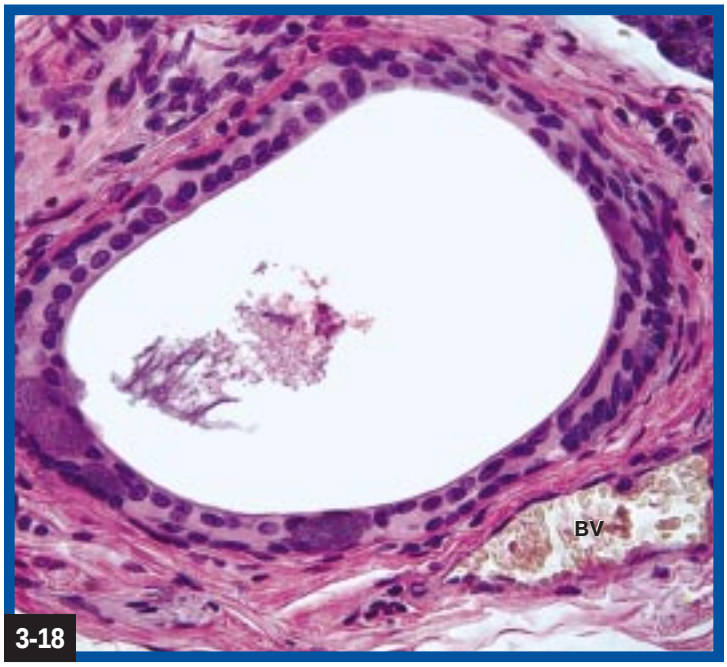
THICK KERATINIZED STRATIFIED SQUAMOUS EPITHELIUM This specimen is from palmar skin. Notice the absence of nuclei in the thick keratinized layer (K). Also, notice the wavy basement membrane (BM) typical of this epithelium—so typical, in fact, that it is often identifiable at low power without even seeing the individual cells. *(X50)*



MORE THICK KERATINIZED STRATIFIED SQUAMOUS EPITHELIUM In this higher magnification, some cell and nuclear outlines are still visible in the keratinized layer (K). Notice the wavy basement membrane and the prickly appearance of the living cells due to intercellular attachments (desmosomes). Also, notice the abundant blood vessels (BV) in the deeper connective tissue and their absence in the epithelium—remember that epithelia are avascular. The simple squamous endothelium of the blood vessels is also visible. *(X210)*



NONKERATINIZED STRATIFIED SQUAMOUS EPITHELIUM In this specimen from the vagina, the cells are flat at the surface and are still alive, as evidenced by the presence of nuclei. (The slight shredding of the surface is not a keratinized layer—the cells are alive.) The wavy basement membrane is also visible. *(X100)*



STRATIFIED CUBOIDAL EPITHELIUM Ducts of glands may be lined with a stratified cuboidal epithelium. This stratified epithelium is only two cells thick. Notice the simple squamous endothelium of the blood vessel (BV) in the lower right corner of the field. *(X320)*

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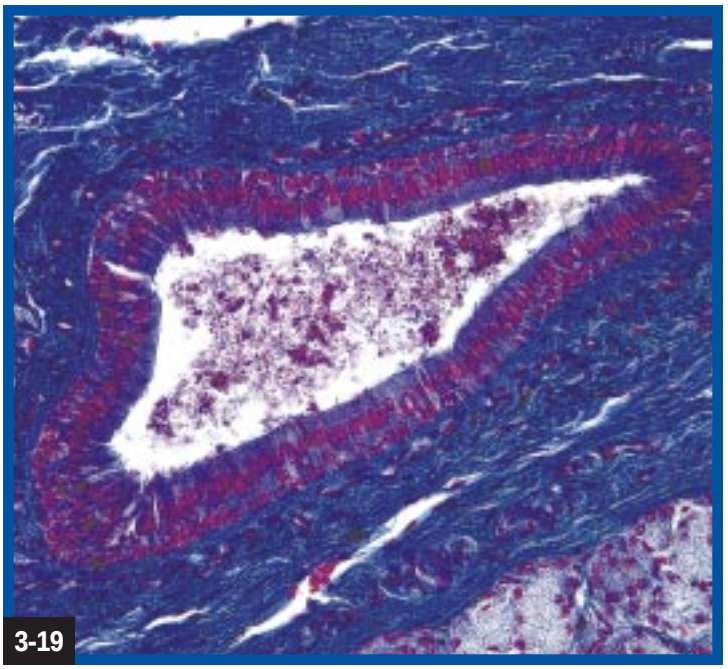
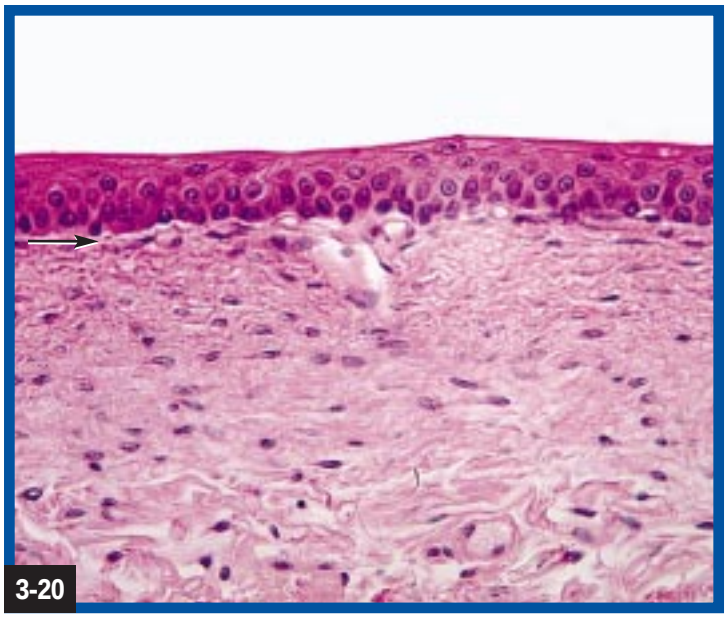
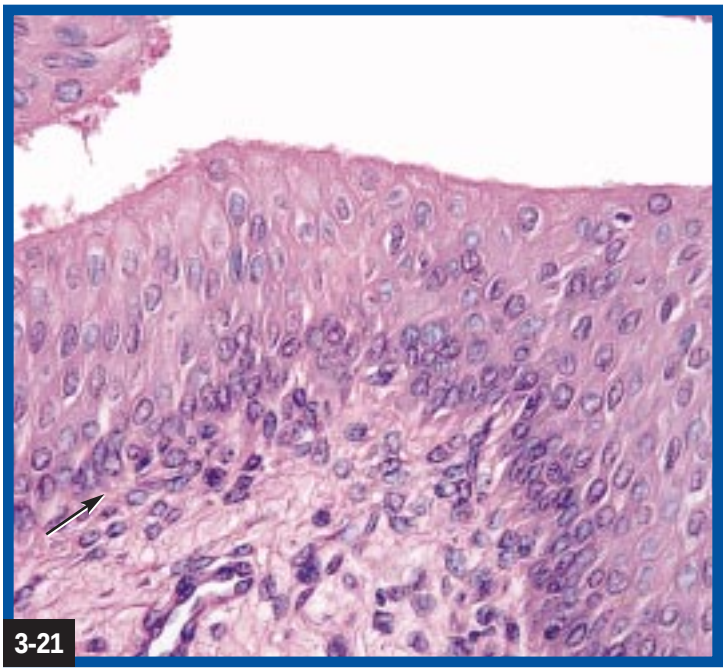


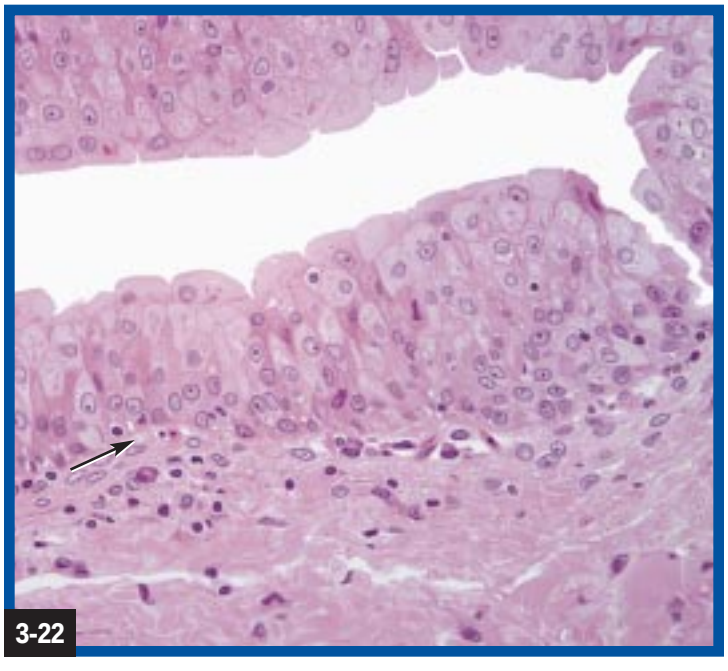
STRATIFIED COLUMNAR EPITHELIUM Larger ducts of glands may be lined with a stratified columnar epithelium. Notice that the basal cells are cuboidal and only the surface layer is columnar. *(X210)*



TRANSITIONAL EPITHELIUM—STRETCHED Transitional epithelium is stratified and is found in the urinary bladder and ureters. It is specialized for stretching. When stretched, the cells flatten, as in this micrograph. This might be confused with stratified squamous, but notice the straight basement membrane (arrow). *(X210)*



TRANSITIONAL EPITHELIUM—RELAXED When the urinary bladder empties, the wall relaxes and the epithelium assumes the shape shown in this micrograph. Most of the cells are vertically elongated and the apical edge of the surface cells is rounded. The arrow indicates the level of the basement membrane. *(X320)*



MORE TRANSITIONAL EPITHELIUM—RELAXED The rounded apical surface of the superficial cells is prominently displayed in this specimen of transitional epithelium. The arrow indicates the level of the basement membrane. *(X210)*

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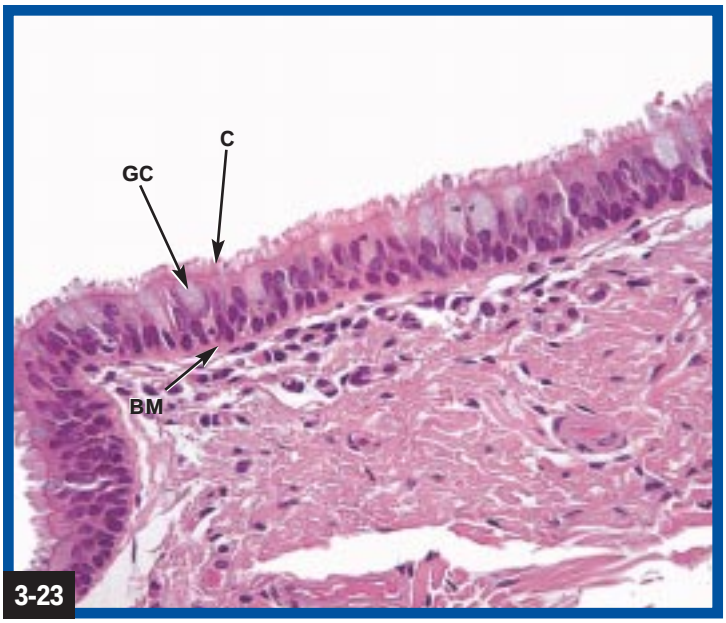
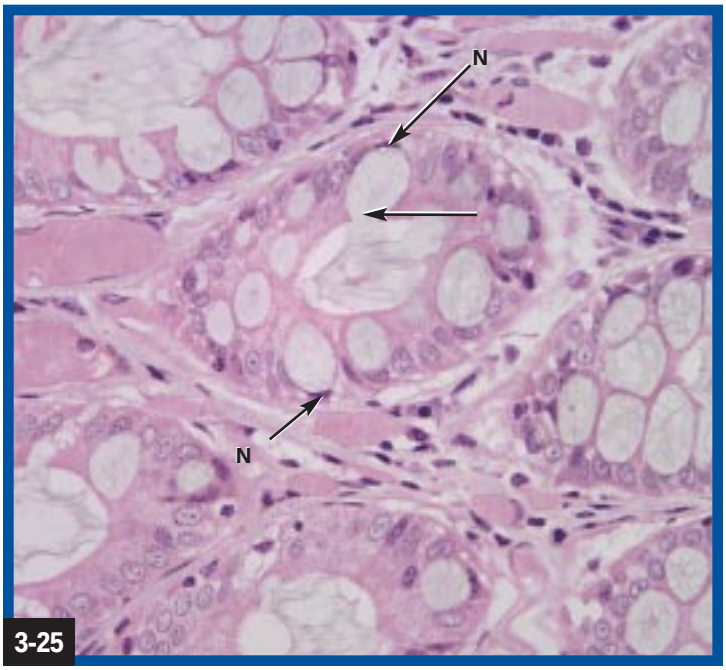


PSEUDOSTRATIFIED CILIATED COLUMNAR EPITHELIUM (PSCC) PSCC is found in the respiratory tract. This specimen is from the trachea. Short, intermediate, and tall cells, all of which touch the basement membrane, characterize it. It is the various heights of nuclei that give the impression of a stratified epithelium. Also present are cilia (C) on the tallest cells, mucus secreting goblet cells (GC), and a prominent basement membrane (BM). *(X320)*

ANOTHER PSCC Since the actual cell boundaries are not very clear in this specimen of PSCC, one might confuse this with a stratified columnar epithelium. However, stratified columnar epithelium usually has only a couple of cell layers and the nuclear layers are fairly distinct, not jumbled as in this micrograph. Globlet cells (GC), cilia (C), and the basement membrane (BM) are clearly shown. *(X320)*



GOBLET CELLS OF THE COLON The numerous goblet cells in the colon's simple columnar epithelium are visible. One cell, indicated by the arrow, has released its secretion, mucin, which when hydrated becomes mucus. Flat, dense staining goblet cell nuclei (N) are visible below the mucin droplets in a couple of cells. *(X320)*

GOBLET CELLS STAINED BY PAS METHOD Due to their high polysaccharide content, the mucin granules of the goblet cells (GC) are PAS positive and appear red. Also notice the basal nuclei (N) of the goblet cells and the brush border (BB) on the simple columnar epithelium. This specimen is from the small intestine. *(X530)*

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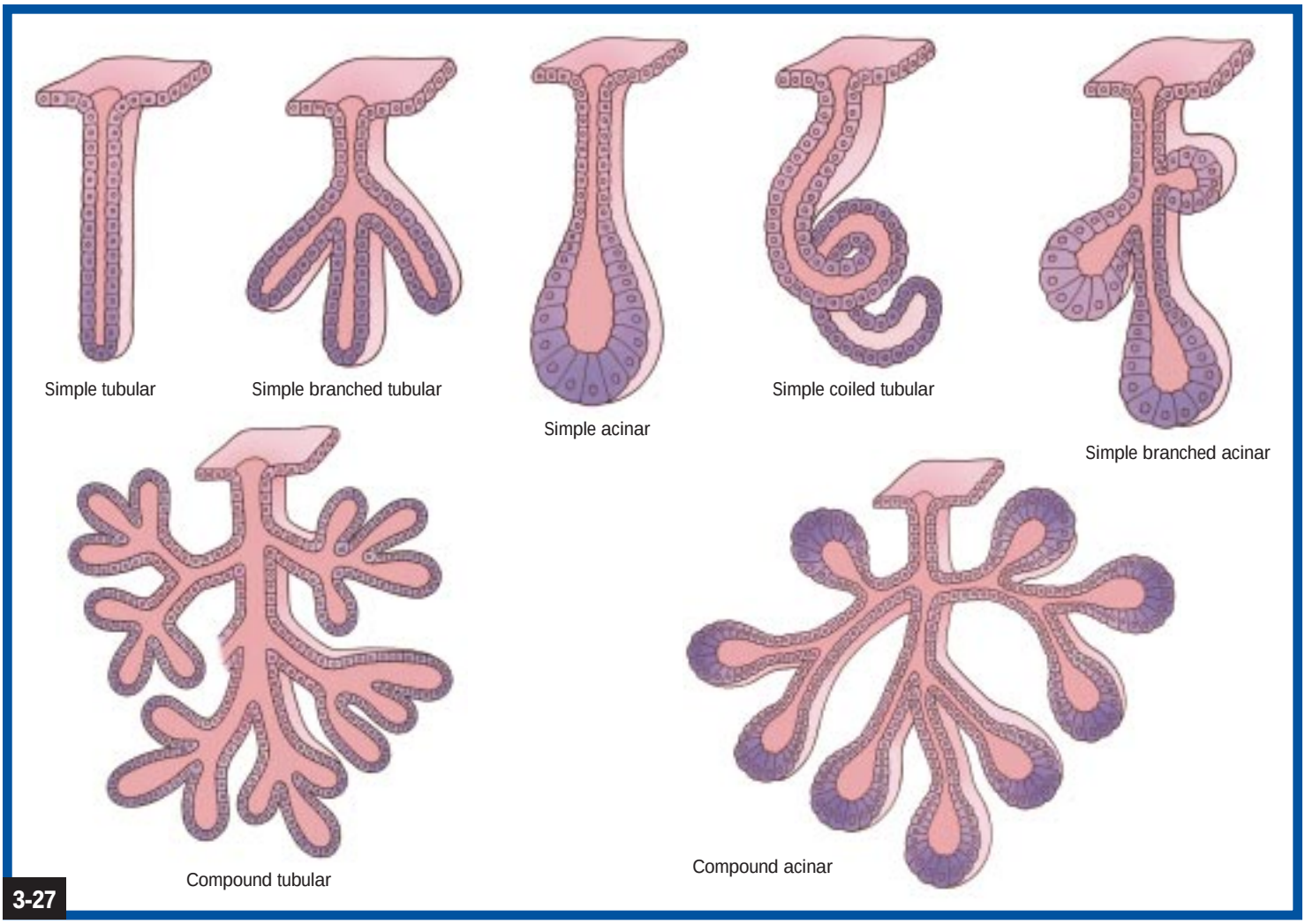
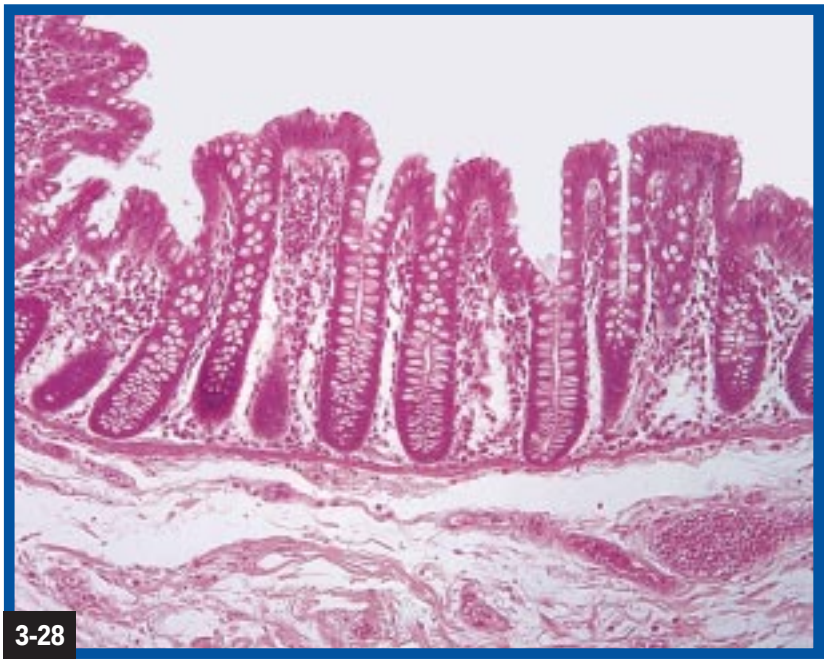


3-27

MULTICELLULAR GLANDS Multicellular glands are composed of a duct (lighter purple) and a secretory portion (darker purple). If the duct is unbranched, the gland is simple; if branched, the gland is compound. In tubular glands, the secretory cells are about the same size as the duct cells. If the secretory cells are larger than the duct cells, the gland is alveolar or acinar. All combinations of simple/compound and tubular/acinar glands are possible.



3-28

SIMPLE TUBULAR GLANDS OF THE COLON The crypts of Lieberkühn in the colon are simple tubular glands. The simple columnar epithelium also has abundant goblet cells. *(X100)*

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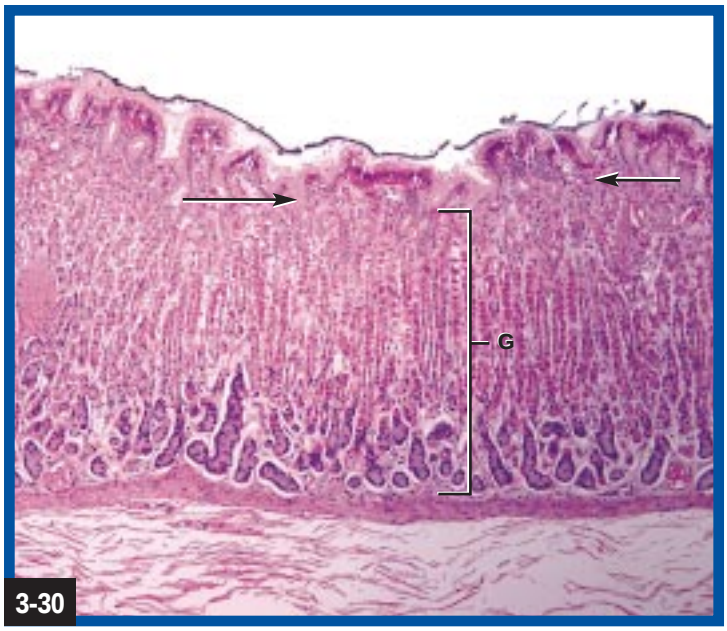
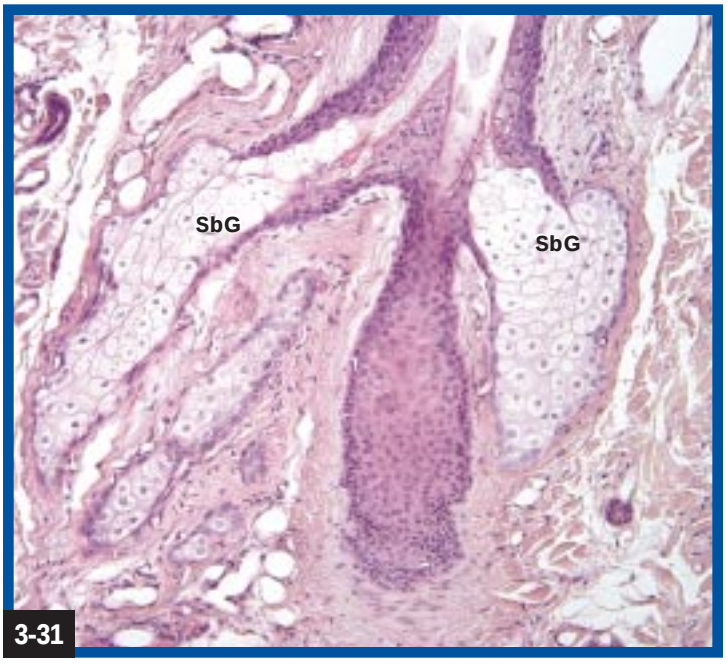
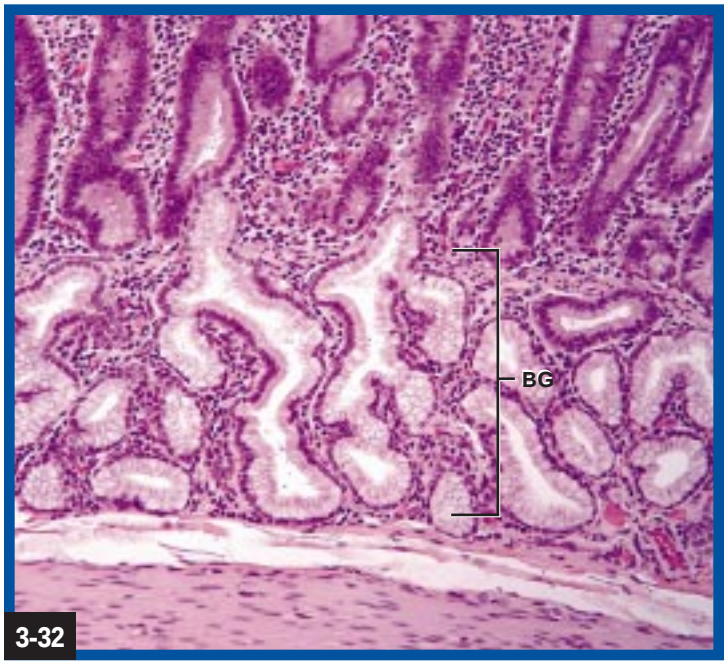
COILED TUBULAR GLAND OF THE SKIN A relatively straight duct (D) connects the coiled secretory part of a sweat gland (SwG) to the skin's surface. Several sweat glands and their ducts are visible in this field. Also note the keratinized stratified squamous epithelium. *(X50)*



BRANCHED TUBULAR GLANDS The mucosal glands of the stomach (gastric glands) are branched tubular glands (G). The straight, tubular nature of the glands is apparent even at this magnification. Several glands branch off each mucosal depression at the level of the arrows and extend to the base of the mucosa. *(X50)*



BRANCHED ACINAR GLAND Sebaceous glands (SbG), associated with hair follicles, are branched alveolar glands. Two glands connected to the follicle are shown in this field. On the left are pieces of other branches that connect in a different plane. The secretory cells release their secretion by disintegrating, which is apparent in this specimen. *(X100)*



COMPOUND BRANCHED TUBULAR GLAND Mucus secreting Brünner's glands (BG) of the duodenum are compound branched tubular glands—that is, both the ducts and secretory parts are branched. The glands are the lighter staining cells in the middle third of the field. Their uniform diameter and branching are apparent in this specimen. Notice the goblet cells in the simple columnar epithelium. *(X100)*

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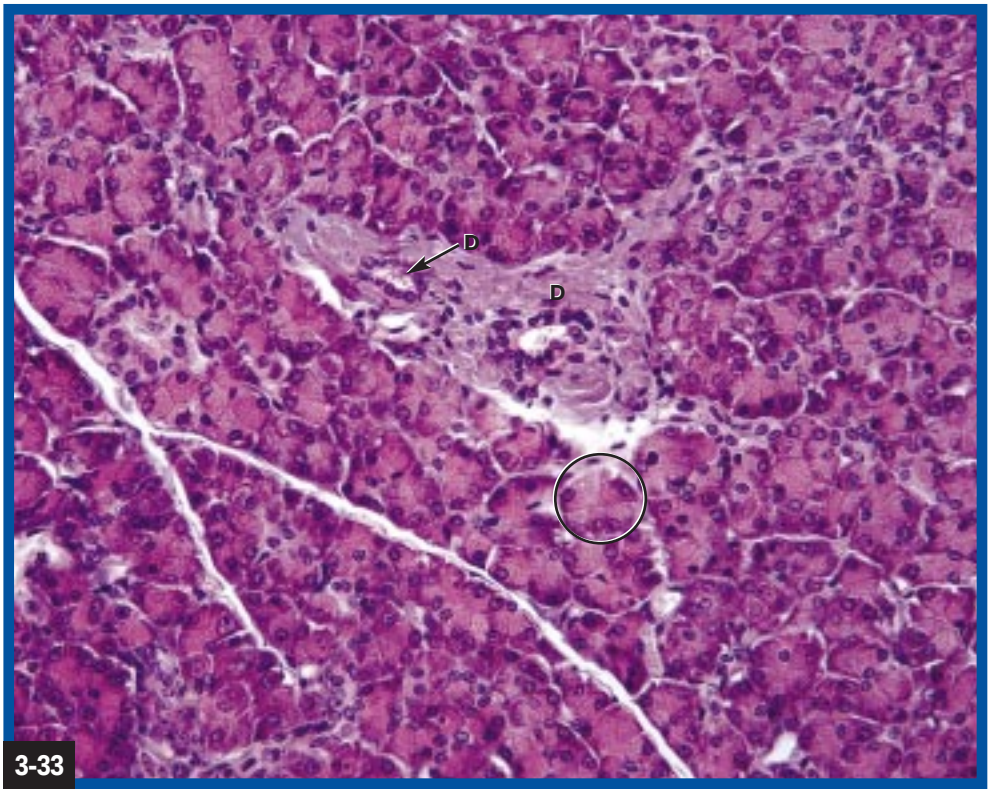
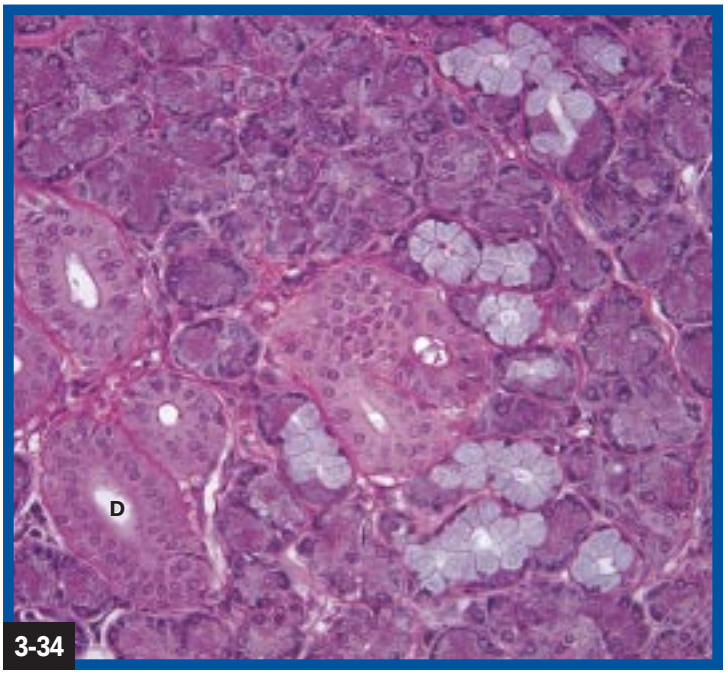
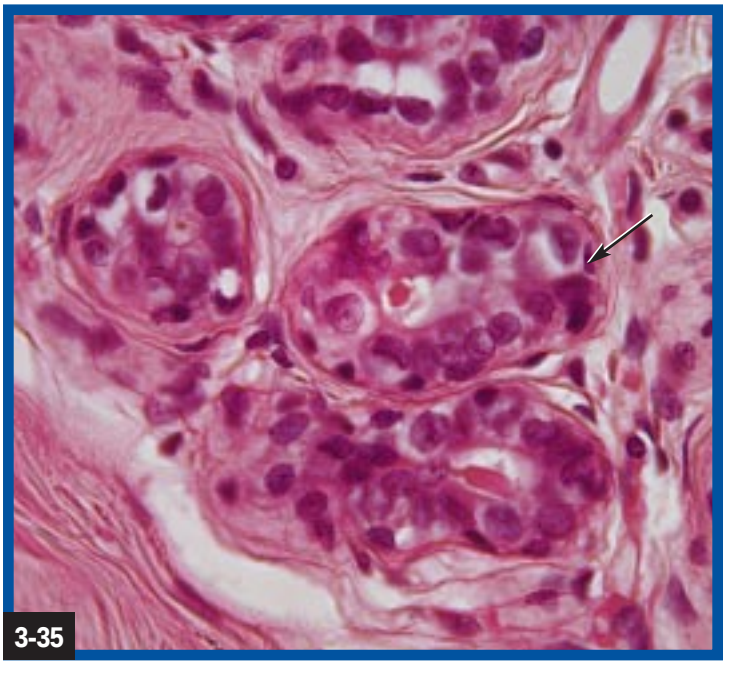


COMPOUND ACINAR GLAND The exocrine portion of the pancreas is made of compound acinar glands. The smaller of the two ducts (D) visible in the center of the field is probably a branch of the larger one. Clusters of secretory cells called acini surround the ducts. One acinus is circled. *(X250)*



COMPOUND TUBULOACINAR GLAND This salivary gland has tubular and acinar secretory portions, as well as numerous branched ducts. The gray secretory cells produce mucus, whereas the darker, more granular cells produce enzymes. The ducts (D) are lined with a simple columnar epithelium and have an obvious lumen. *(X200)*



MYOEPITHELIAL CELLS In sweat glands (as in this specimen) and salivary glands, myoepithelial cells (arrow) occupy the region between the secretory cells and the basement membrane. Their contraction assists movement of the secretion into the duct. *(X530)*

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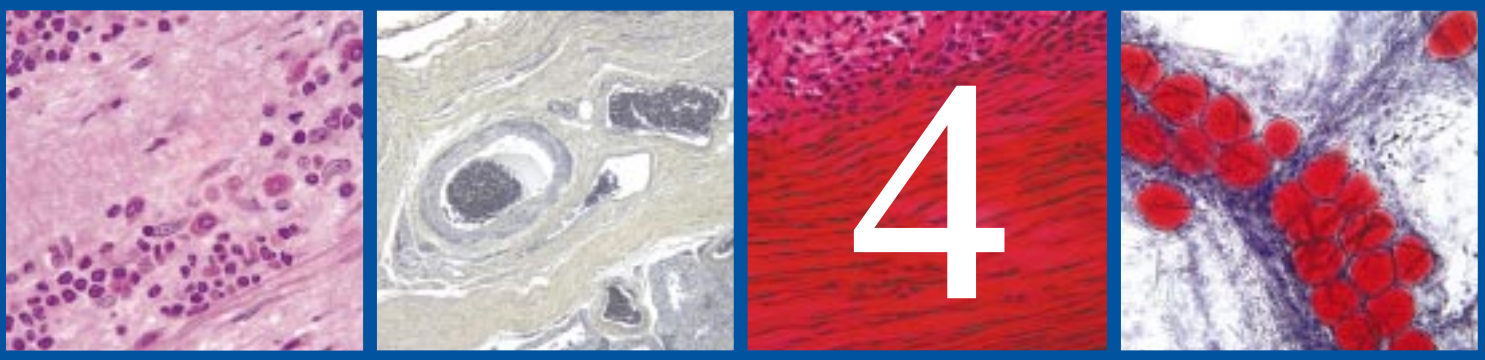
Fibrous Connective Tissues

CHAPTER



Basic Characteristics of Connective Tissues

Connective (supporting) tissues anchor organs and join the other tissues of the body into a structurally integrated whole. In fact, most organs have a connective tissue covering that often penetrates it and binds the whole organ together. Unlike epithelia, connective tissues generally have abundant **extracellular (intercellular) matrix** and relatively few cells. The matrix consists of protein fibers, a ground substance, and other supporting biochemicals. Connective tissues may be vascular or avascular.

Fibrous connective tissues (Connective Tissue Proper) are the subject of this chapter. Cartilage and bone are covered in Chapter 5, and Blood and Bone Marrow are covered in Chapter 6.

Functions of Fibrous Connective Tissues

The functions of fibrous connective tissues are many and varied. Some examples are:

- Binding and support (*e.g.*, ligaments)
- Defense (*e.g.*, macrophages and mast cells of various tissues)
- Storage (*e.g.*, adipose tissue)
- Transport of materials between blood and other tissues (*e.g.*, tissue fluid in loose connective tissue and others)

Embryonic Connective Tissues—Mesenchyme and Mucous Tissue

Connective tissues of the adult are derived from an embryonic tissue called **mesenchyme** (Figure 4-1), which is derived from embryonic mesoderm. The cells of mesenchymal tissue are unspecialized and have the potential to differentiate into the cells typical of adult connective tissues (Figure 4-2). Further, adult connective tissues appear to retain some mesenchymal cells that act as a source of cells in case repair is necessary. (Some authors attribute the source of cells to **pericytes** found associated with capillaries.) Mesenchymal cells are angular or spindle-shaped and form a loose mesh that is functionally a rudimentary connective tissue. Fibers are absent.

Mucous tissue (Figure 4-3) is found only in the umbilical cord and a few other places in the embyro. It has fibroblasts and very few fibers coursing through a jelly-like ground substance (Wharton's jelly).

Extracellular Matrix of Adult Connective Tissues

The properties of a connective tissue are largely due to the properties of its matrix. Comprising matrix are the ground substance, fibers, and structural glycoproteins.

Ground substance is an amorphous, gel-like material composed of charged glycosaminoglycans—GAGs—(mucopolysaccharides) and proteoglycans (mucoproteins) of various types. Both are polymers of disaccharide subunits, but the latter are also bonded to proteins. Their charges make them hydrophilic, resulting in tissue fluid mixing readily with the ground substance and helping create the gel-like state. Because of this association, the ground substance is an essential participant in the transport of nutrients and wastes between the blood and other tissues. Ground substance is not easily visualized in histological preparations.

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Fibers are made of protein and come in two basic types: collagen and elastic. **Collagen fibers** (Figure 4-4) are made of the protein collagen and are the primary fibers of connective tissues. At least 19 types of collagen have been identified. All exhibit a high tensile strength and are inelastic. **Type III collagen fibers** (Figure 4-5) are thin and branched, and were formerly known as **reticular fibers**. These fibers form a framework of the liver, lymphatic tissue and bone marrow. **Elastic fibers** (Figures 4-4, 4-6, and 4-7) are made of the protein elastin. The elasticity they confer is an important property of organs that can be deformed and then return to their original shape, such as larger arteries and the skin.

Structural glycoproteins are involved in anchoring and fastening cells to extracellular material, including basement membranes.

Cells of Adult Connective Tissues

There are many cell types in fibrous connective tissues. Fibroblasts, mast cells, macrophages, adipocytes, lymphocytes and plasma cells are the most commonly encountered ones.

Fibroblasts (Figures 4-4, 4-6, and 4-8) are derived from mesenchymal cells and are responsible for synthesis and maintenance of the matrix. They are elongated in the direction of fiber orientation and have a granular nucleus with a prominent nucleolus.

Macrophages (Figure 4-9) are derived from blood monocytes and are found in a variety of tissues. Their function is to *phagocytose* (engulf) foreign, dead and dying cells, and cellular debris. In their role as **antigen presenting cells (APCs)** they present antigens to lymphocytes as part of the immune response. **Resident (fixed) macrophages** (Figure 4-9a) are regular inhabitants of a particular tissue whereas **elicited (wandering** or **free) macrophages** (Figure 4-9b) circulate in the blood and migrate to where they are needed. In the light microscope, macrophages have an irregular shape, a basophilic, finely granular cytoplasm, and an oval- to kidney-shaped nucleus.

Mast cells (Figure 4-10) originate in the bone marrow, but occupy various connective tissues. In many ways, they resemble blood basophils, but are not developmentally related to them. They are large with prominent cytoplasmic membrane-bound granules. The granules contain chemicals (such as heparin, histamine, chemotactic factors, and many others) which are involved in the inflammatory response. Release of the granules' contents is called *degranulation*.

Adipocytes are derived from mesenchymal cells and, perhaps, fibroblasts. They are specialized to store fat. **Unilocular fat cells** (Figure 4-11) store the fat as a single, large droplet that pushes the nucleus and cytoplasm to the cell's periphery. Often, the fat is dissolved from the adipocytes during slide preparation, so all that is seen is empty cells (Figure 4-11b). **Multilocular fat cells** (Figure 4-12) are smaller, store fat in many droplets, and have a spherical nucleus.

Other leukocytes (white blood cells) of various types may be seen in connective tissues, especially at the site of infection or inflammation. Most commonly seen in healthy tissue preparations are **lymphocytes** and **plasma cells** (Figures 4-13 and 4-14). Lymphocytes have a dark staining nucleus surrounded by a thin layer of cytoplasm. Plasma cells are derived from lymphocytes and secrete antibodies. They have a purplish cytoplasm (due to abundant RER necessary for antibody production) and an eccentric nucleus. A pale region next to the nucleus may also be visible. It is the site of the Golgi apparatus. **Neutrophils** have a granular cytoplasm and a segmented nucleus. They are phagocytic.

Classification of Adult Fibrous Connective Tissues

Fibrous connective tissues have traditionally been classified according to the arrangement and density of fibers. **Regular connective tissues** have the fibers oriented in the same direction; the fibers of **irregular connective tissues** are oriented in all directions. The fibers of **loose connective tissues** occur singly, whereas the fibers of **dense connective tissue** occur in bundles and are tightly packed together. While these categories will be used here, it should be realized that they represent extremes and that intermediate connective tissue types exist. Further, some authors consider **adipose tissue** and **reticular tissue** as loose connective tissues, but they will be considered separately in this chapter.

Loose Areolar Tissue

Loose areolar tissue (Figures 4-4, 4-6, 4-8, 4-15 and 4-16) is the connective tissue component of serous and mucous membranes, acts as filler between muscles and between muscles and skin, and is found in various other locations in the body. Collagen and elastic fibers are present, as are fibroblasts, mast cells, macrophages, and most other connective tissue cells. It is vascular.

Dense Irregular Connective Tissue

Dense irregular connective tissue (Figures 4-17 and 4-18) is characterized by densely packed collagen bundles oriented in all directions. It is vascular and fibroblasts are the predominant cell type. It comprises the dermis and capsules of many organs.

Dense Regular Connective Tissue

Dense regular connective tissue is an avascular tissue that has fiber bundles arranged in parallel fashion. This fiber arrangement confers great tensile strength on the tissue. Fibroblasts are compressed and appear elongated between the compact fibers.

Tendons provide an example of **dense regular collagenous connective tissue** (Figure 4-19). **Dense regular elastic**

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connective tissue has an abundance of elastic fiber bundles and is found in larger blood vessels and some vertebral ligaments (Figure 4-20).

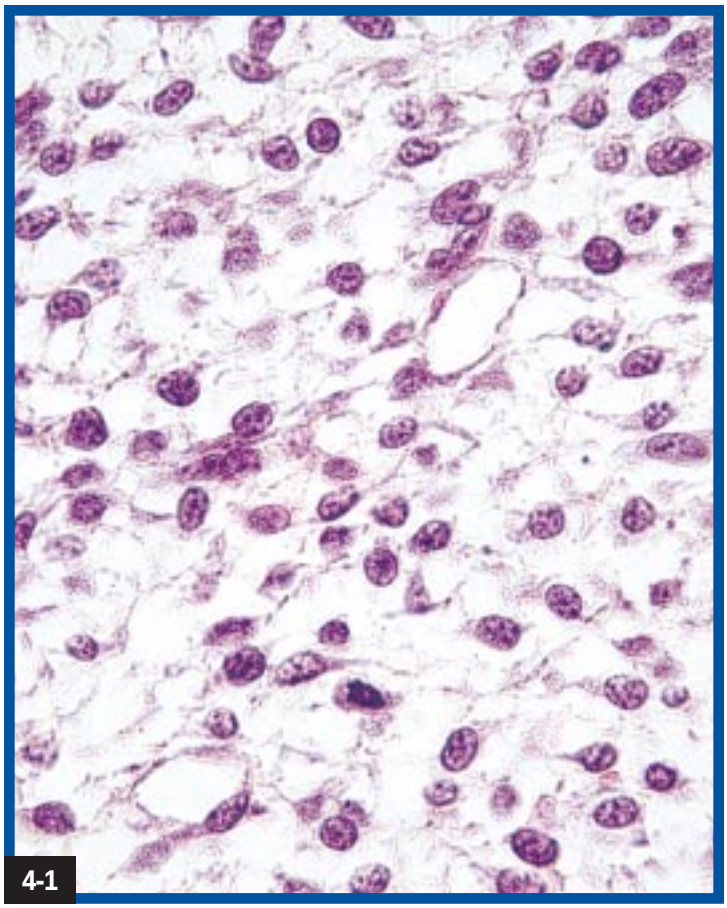
Adipose Tissue

Adipose tissue is a vascular tissue and differs from other connective tissues in that it is very cellular with little intercellular material. **White adipose tissue** (Figures 4-11 and 4-21) is composed of unilocular adipocytes and is commonly found in the subcutaneous regions as well as in serous membranes. Fixing slides by standard methods dissolves the fat, so "empty" adipocytes are what are typically seen. In some procedures, the fat is retained and can be stained, as with the oil-soluble dye Sudan red (Figure 4-11a).

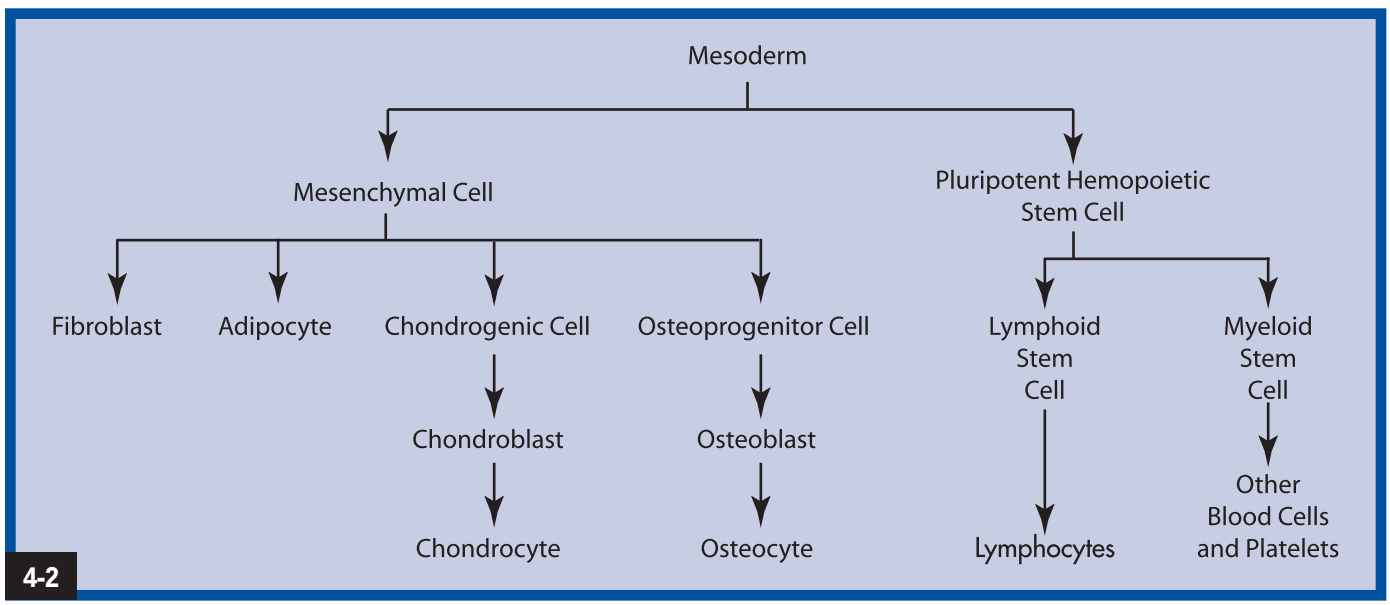
Brown adipose tissue (Figure 4-22) is present in the embryo and possibly persists in modified form in the adult. It is composed of multilocular adipocytes and is much more vascular than white adipose tissue. It is involved in generation of body heat.

Reticular Connective Tissue

Reticular connective tissue (Figure 4-23) is a loose connective tissue with an abundance of reticular fibers (Type III collagen). The fibers are not stained with H&E, but can be visualized with silver stains. Reticular connective tissue forms the framework of bone marrow, lymphoid organs, and the liver sinusoids.



MESENCHYME Mesenchymal tissue is a primitive connective tissue lacking in fibers. Its cells are angular and have the potential to develop into more specialized connective tissue cells. *(X610)*



SCHEME OF CONNECTIVE TISSUE CELL DEVELOPMENT Connective tissues develop from embryonic mesoderm which gives rise to mesenchymal cells and pluripotent hemopoietic stem cells (HSC). Mesenchymal cells give rise to fibroblasts and adipocytes of connective tissue proper (covered in this chapter), and cartilage and bone cells (covered in Chapter 5). The HSC gives rise to all formed elements in blood (covered in Chapter 6).

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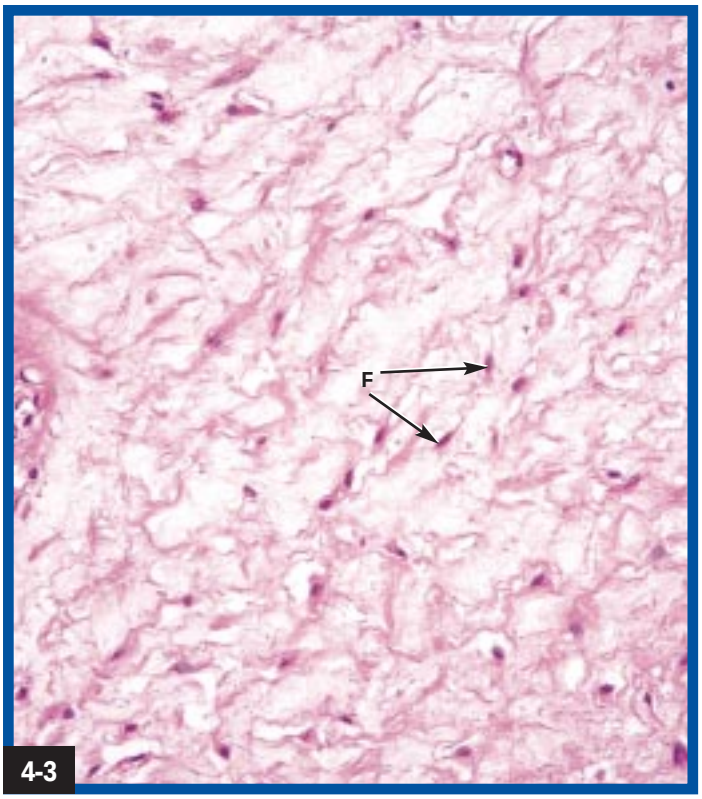
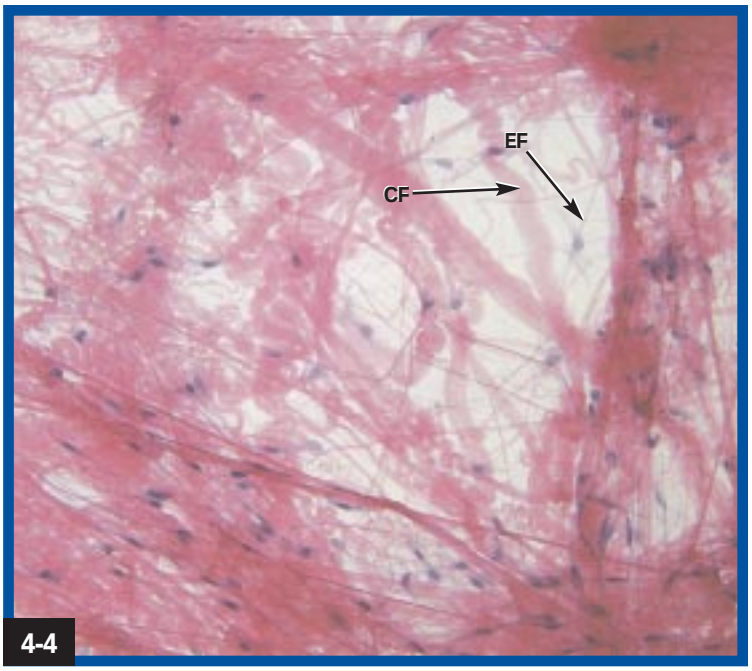
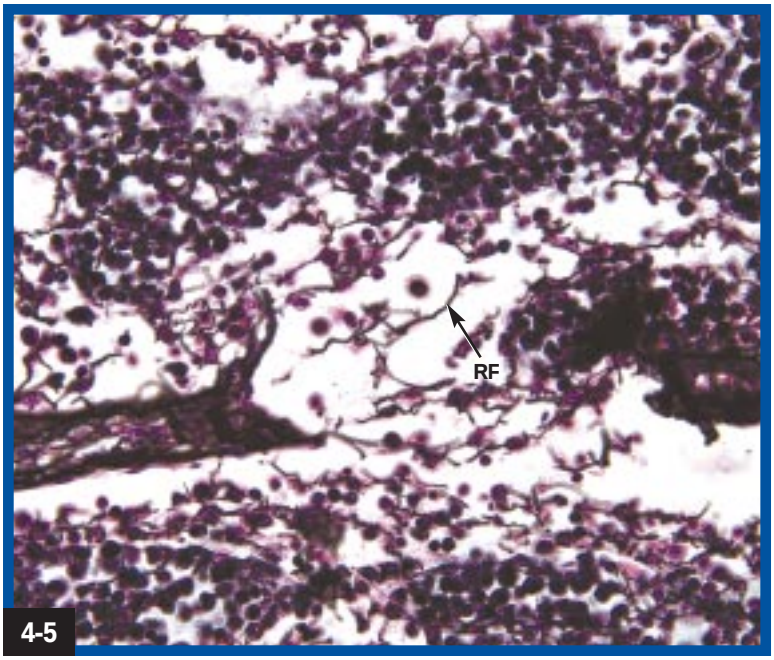


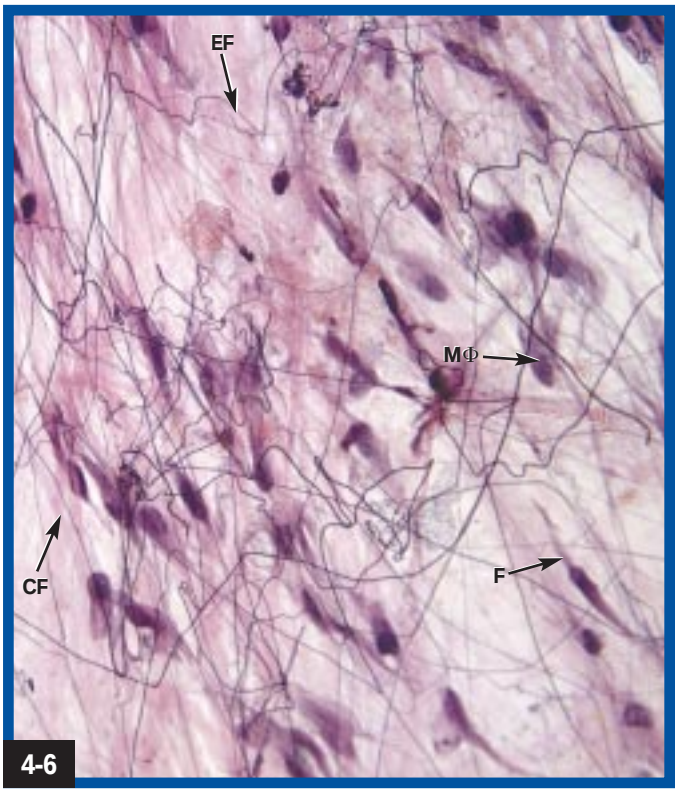
MUCOUS TISSUE Mucous tissue is found only in the umbilical cord and a few other sites in the embryo. It contains fibroblasts (F) and a few fibers, so it is more specialized than mesenchyme. The ground substance is like jelly. *(X380)*



COLLAGEN FIBERS Thick, strong collagen fibers (CF) are seen in this specimen of loose areolar tissue. The thin fibers are elastic fibers (EF), and most of the cells are fibroblasts. *(X100)*



RETICULAR FIBERS (TYPE III COLLAGEN FIBERS) Reticular fibers (RF) are thin and branched. This specimen is a lymph node, but they also form the structural framework of the spleen, bone marrow, and some other organs. These fibers do not show up when stained with H&E; a silver stain must be used to visualize them. *(X320)*



ELASTIC FIBERS IN LOOSE AREOLAR TISSUE The thin, dark lines are elastic fibers (EF) in this loose areolar tissue. Also visible are collagen fibers (CF), fibroblasts (F), and macrophages (MΦ). *(X210)*

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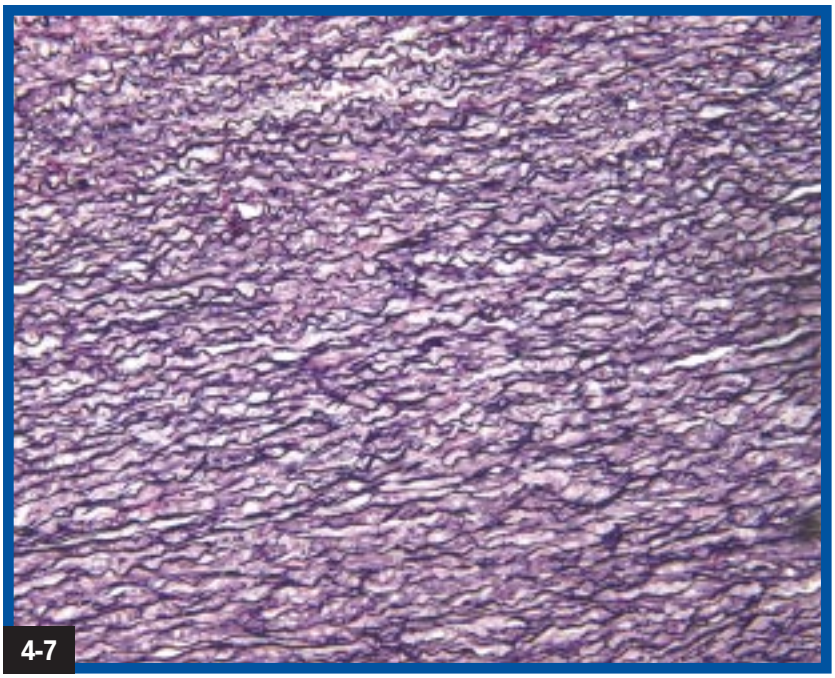
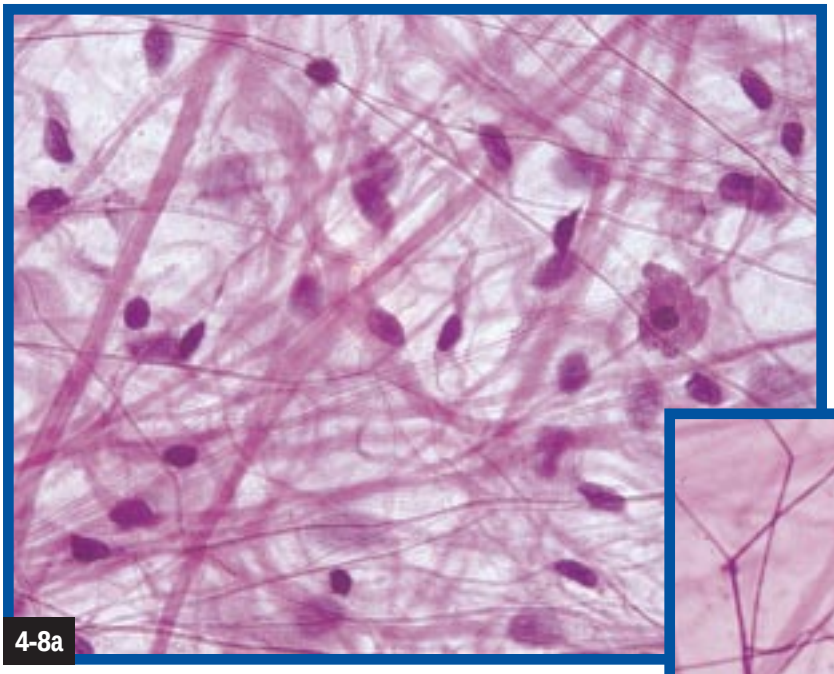
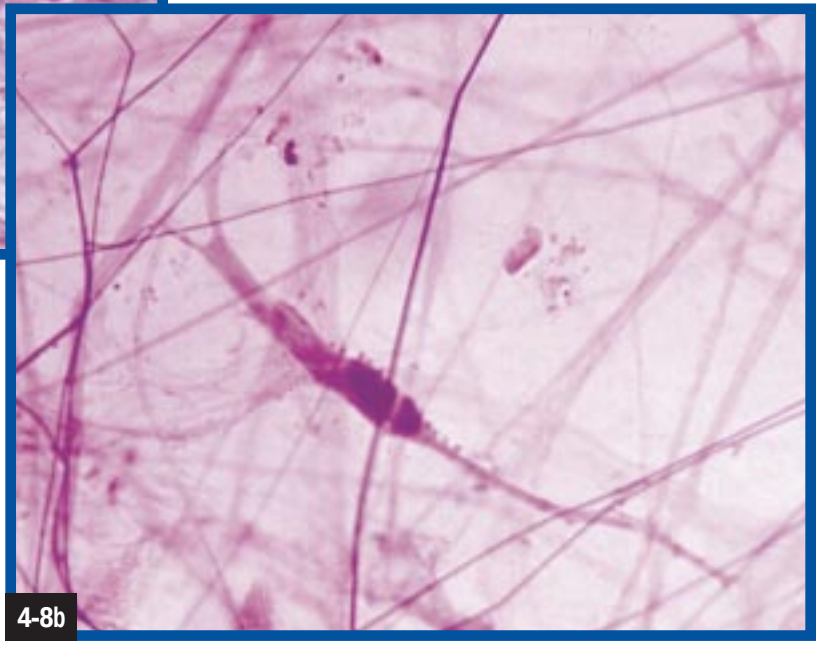


ELASTIC FIBERS IN ELASTIC TISSUE This specimen is from the aorta. Its wall has abundant elastic fibers (dark lines) arranged circularly around the vessel. The elasticity allows the aorta to stretch when blood is pumped into it, then recoil and push the blood further when the heart relaxes. *(X100)*



FIBROBLASTS The most commonly seen cell in fibrous connective tissues is the fibroblast. They have an irregular shape and (usually) a prominent nucleolus. (a) Most cells in this spread of loose areolar tissue are fibroblasts. Collagen and elastic fibers are also visible in this specimen. (*X530*) (b) A single fibroblast illustrating the irregular shape is shown here. *(X760)*



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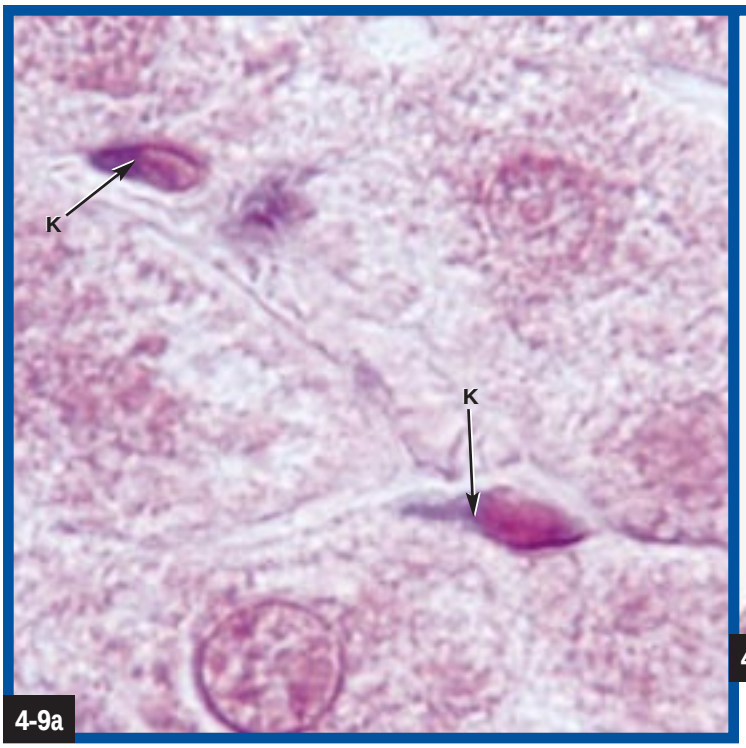
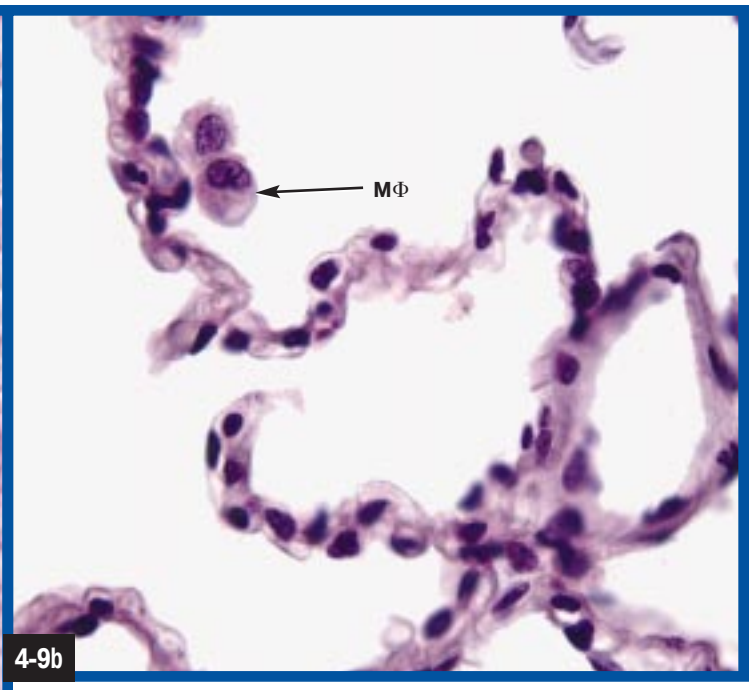
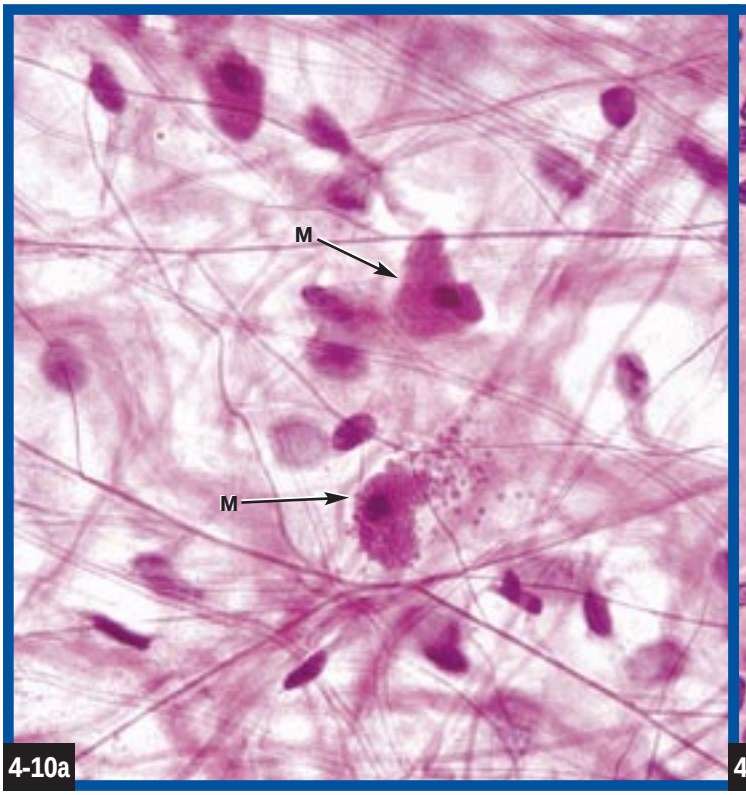
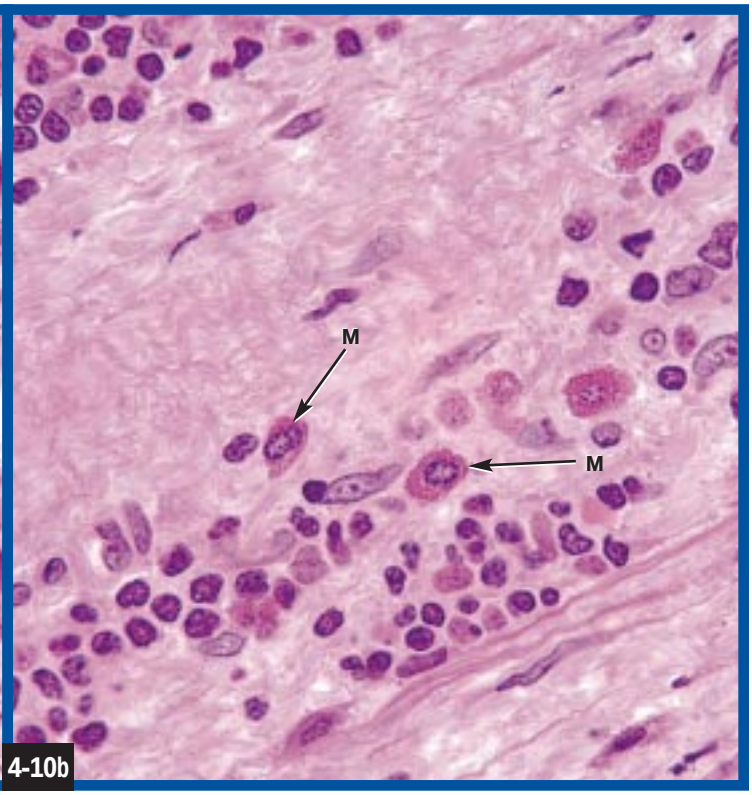




MACROPHAGES Macrophages may either be fixed or wandering. (a) The Kupffer cells (K) are fixed macrophages that line the liver sinusoids and remove material from the blood. These macrophages have ingested a dye that makes them stand out. Fixed macrophages may also be seen in the spleen and lymph nodes. (*X530*) (b) Wandering macrophages (MΦ) are found in the lung. *(X630)*





MAST CELLS Mast cells (M) are involved in the inflammatory response by degranulating and releasing histamine and other chemicals. (a) This is loose areolar tissue with two mast cells shown. The lower mast cell has degranulated. (*X630*) (b) Several mast cells are visible in this tonsil specimen. *(X630)*

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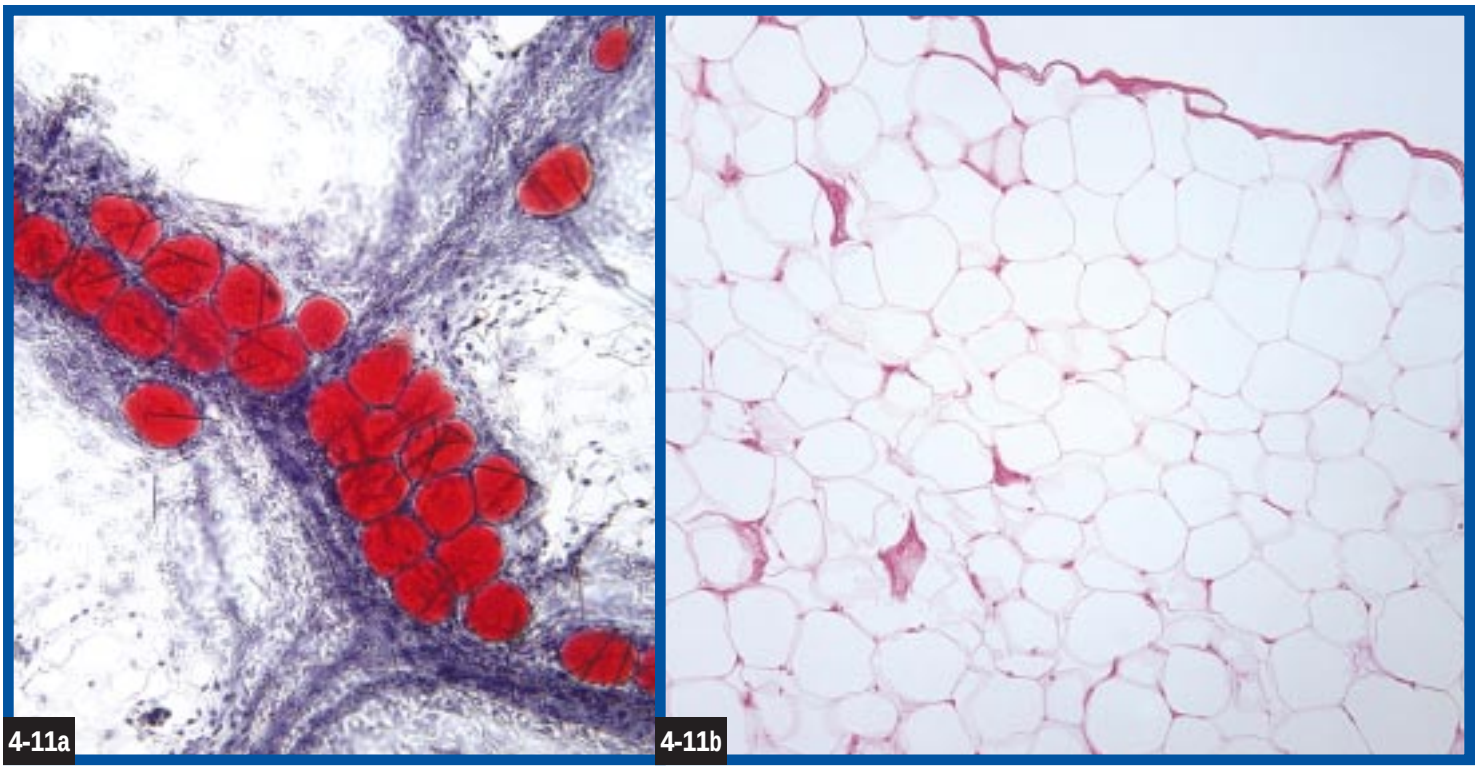
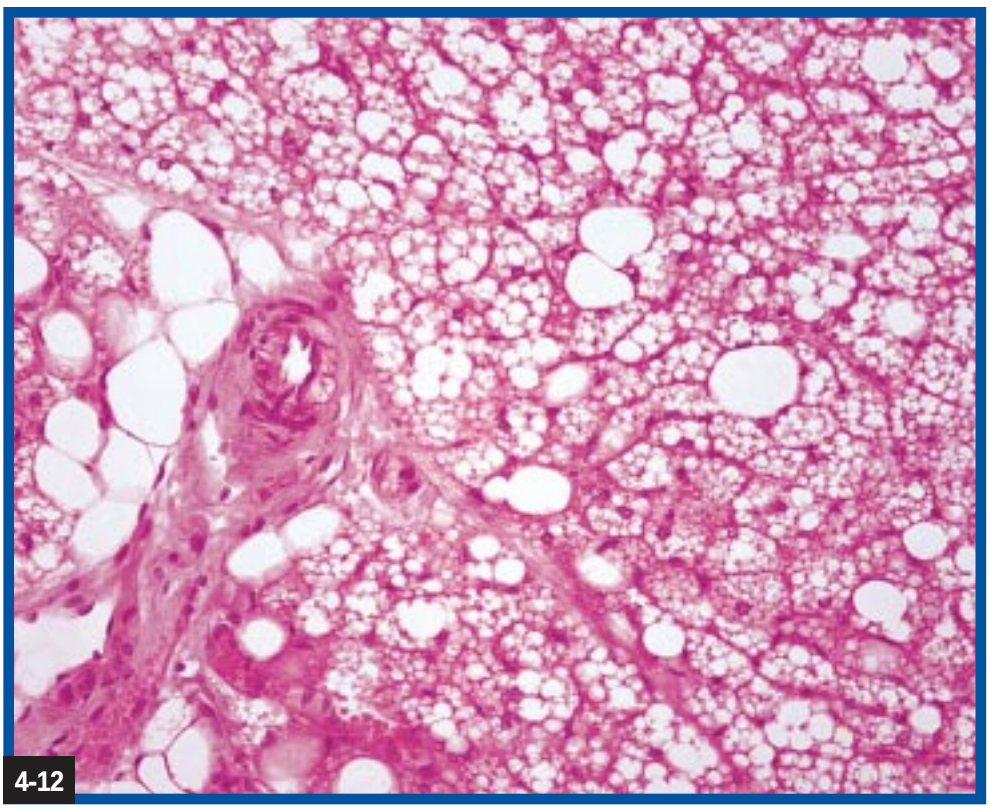


UNILOCULAR ADIPOCYTES The cytoplasm and nucleus of unilocular adipocytes is pushed to the periphery and the single, large fat droplet occupies the majority of the cell. (a) Unilocular adipocytes stained with Sudan Red, a fat-soluble stain that demonstrates the fat droplet. *(X100)* (b) Standard slide preparation dissolves and removes the fat droplet and all that remains of the adipocytes is the membrane and some cytoplasm. *(X100)*



MULTILOCULAR ADIPOCYTES Only human embryos have multilocular adipocytes (although they are found in other adult mammals). The fat is stored as several droplets rather than one big one. *(X250)*

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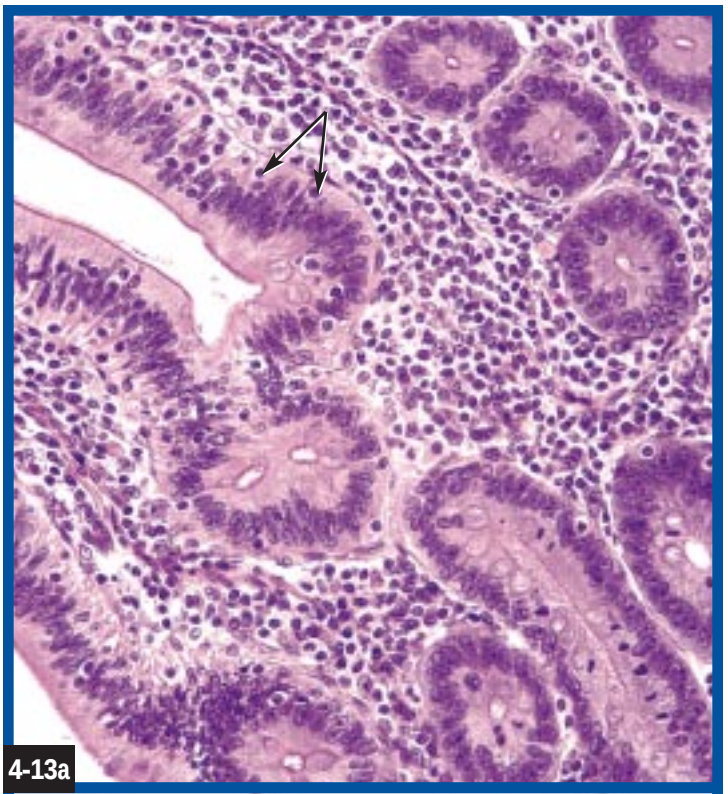
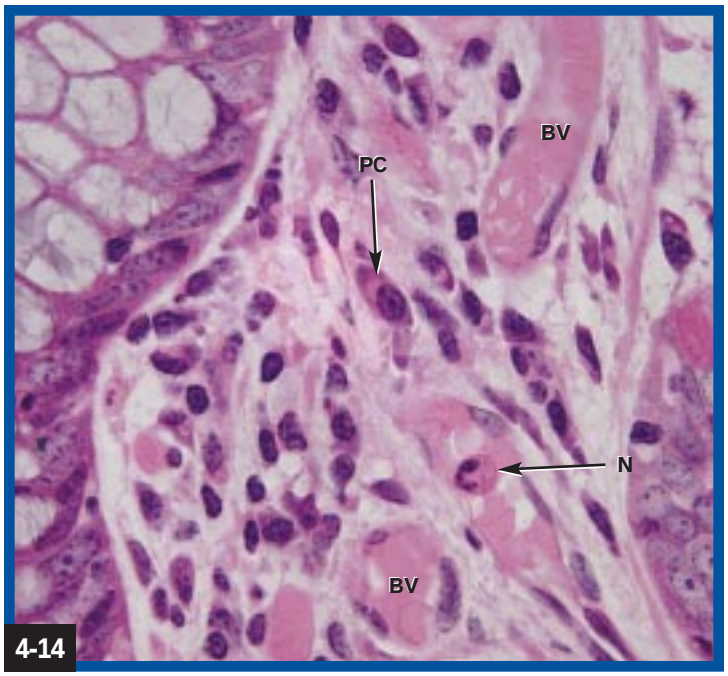


4-13a

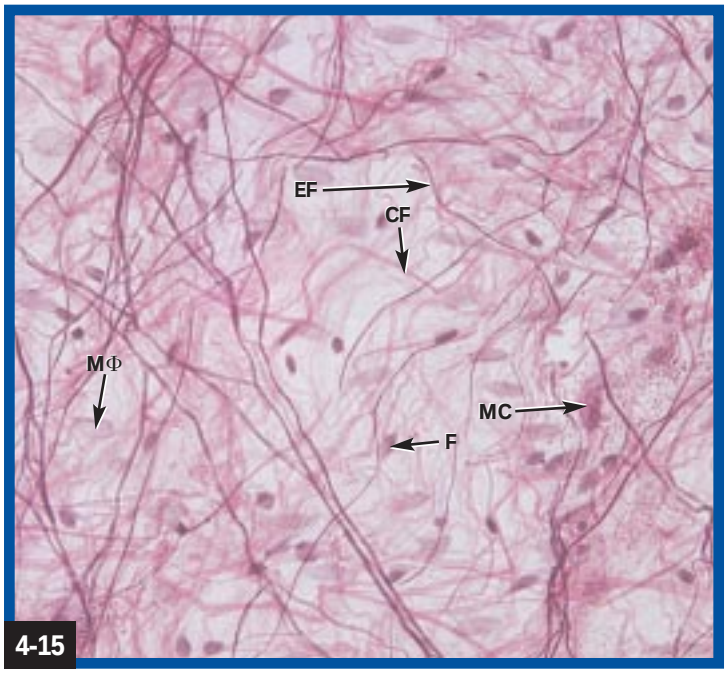
4-13b

LYMPHOCYTES The lamina propria of mucous membranes is often infiltrated with lymphocytes, cells of the immune system that secrete antibodies among other protective functions. They are small, round cells with dark staining nuclei. (a) In this specimen from the small intestine, the lymphocytes are quite dense. Some have even entered the simple columnar epithelium (arrows). (*X250*) (b) This specimen is also from the small intestine, but the lymphocytes (L) in the lamina propria are not as dense. *(X250)*



4-14

PLASMA CELL AND NEUTROPHIL Plasma cells (PC) are lymphocytes that are actively secreting antibodies. They are elongated cells with the nucleus toward one end. The nucleus looks like a clock face because of the chromatin distributed around its periphery. A pale region of cytoplasm near the nucleus is the site of a Golgi apparatus. A phagocytic neutrophil (N) is also visible in the field. Its granular cytoplasm is not very apparent, but the segmented nucleus is. Notice the blood vessels (BV) in the field. *(X630)*



4-15

LOOSE AREOLAR TISSUE A loose weave of collagen (CF) and elastic fibers (EF) characterizes loose areolar tissue (LAT). LAT is found as a supporting tissue and as filler between organs (fascia). Fibroblasts (F), macrophages (MΦ), and mast cells (MC) are visible in this specimen. *(X320)*

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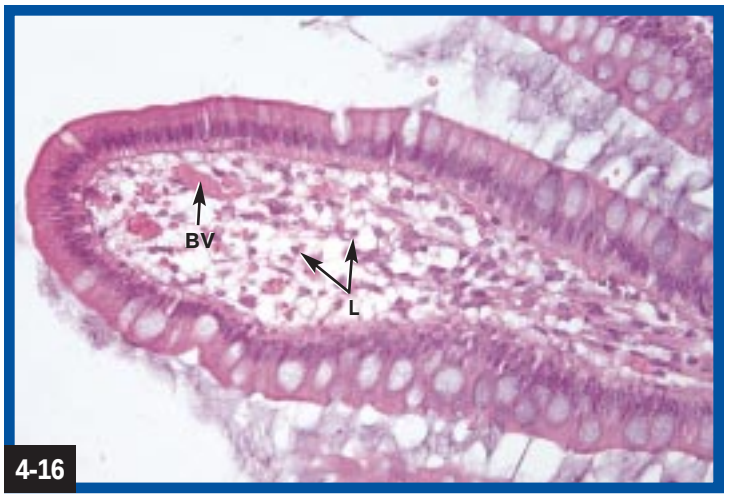
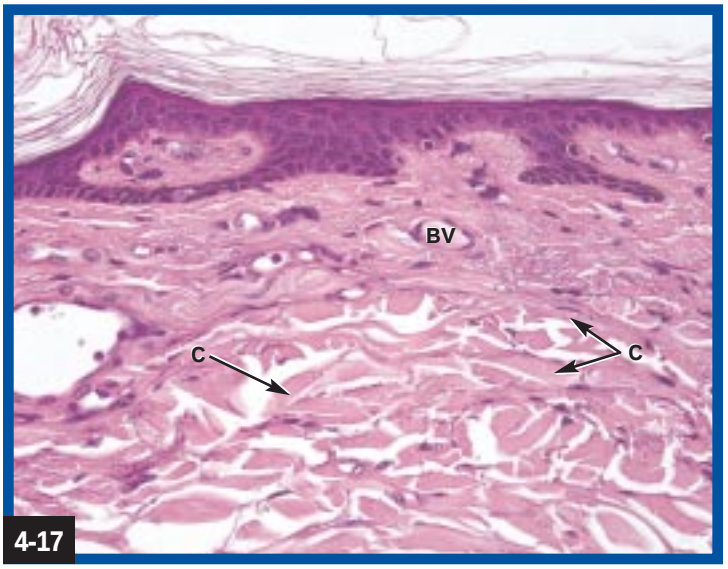
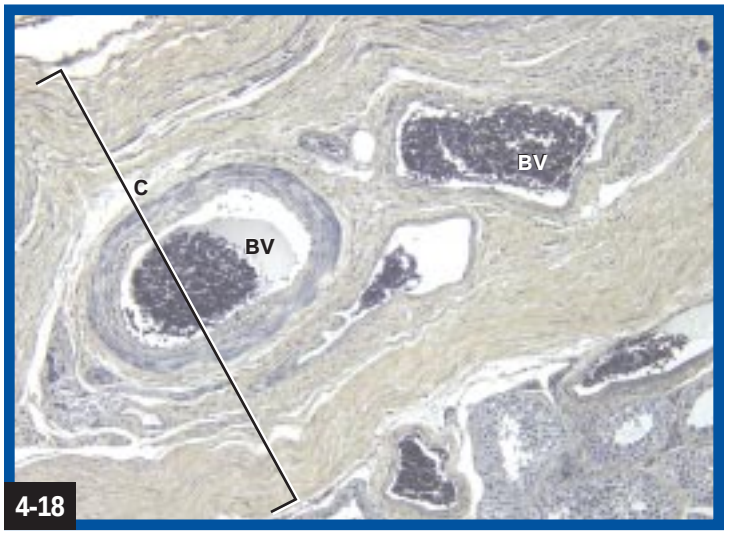
LAMINA PROPRIA Loose fibrous connective tissue comprises the lamina propria of many epithelial membranes. This specimen is from the small intestine. Notice the blood vessels (BV) and lymphocytes (L) in the lamina propria. *(X400)*

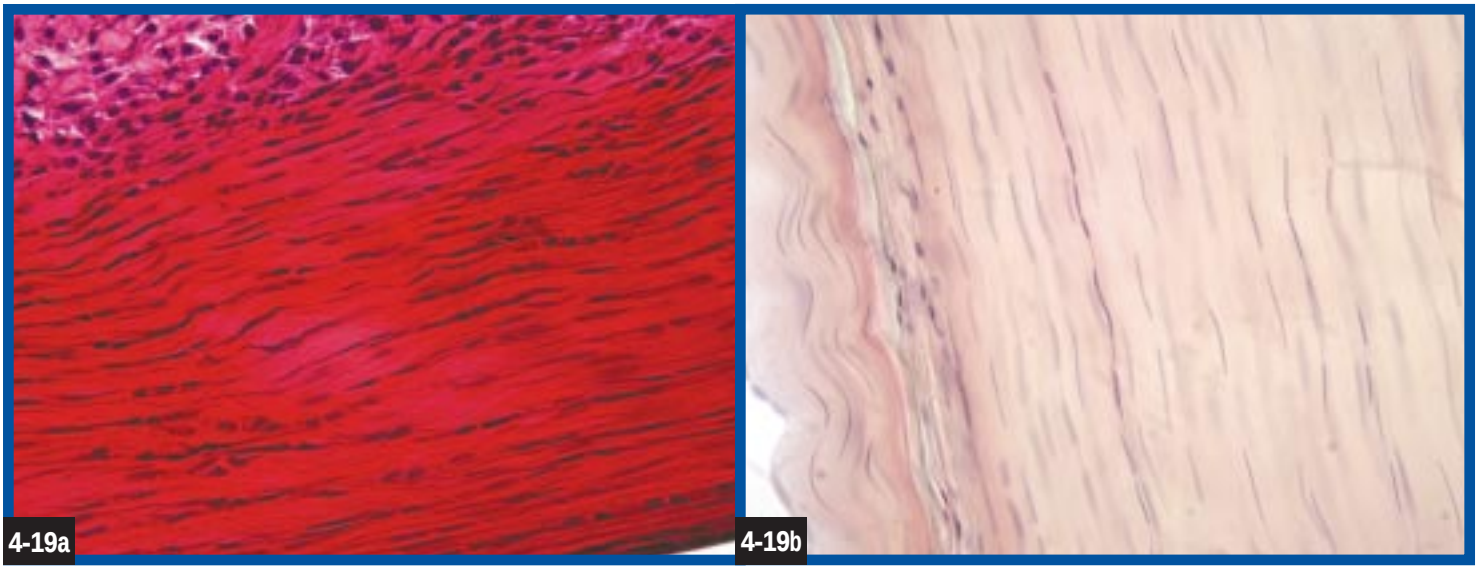




DENSE IRREGULAR CONNECTIVE TISSUE The dermis of the skin is composed of an irregular weave of tightly packed fiber bundles. Although all fiber types are present, collagen bundles (C) are the most obvious. Notice that the bundles are sectioned longitudinally, obliquely, and in cross section, indicating their irregular arrangement. Most of the cells are fibroblasts. Blood vessels (BV) indicate this tissue is vascular. *(X210)*



FIBROUS CAPSULE Many organs, including the testis shown here, are covered by a dense fibrous connective tissue capsule (C). Notice the blood vessels (BV). *(X50)*



COLLAGENOUS DENSE REGULAR CONNECTIVE TISSUE (a and b) Tendons, shown here, and ligaments, are made of closely packed collagen bundles all oriented in the same direction. Dense regular connective tissue is avascular. The cells are fibroblasts, and they are typically in rows. *(X210)*

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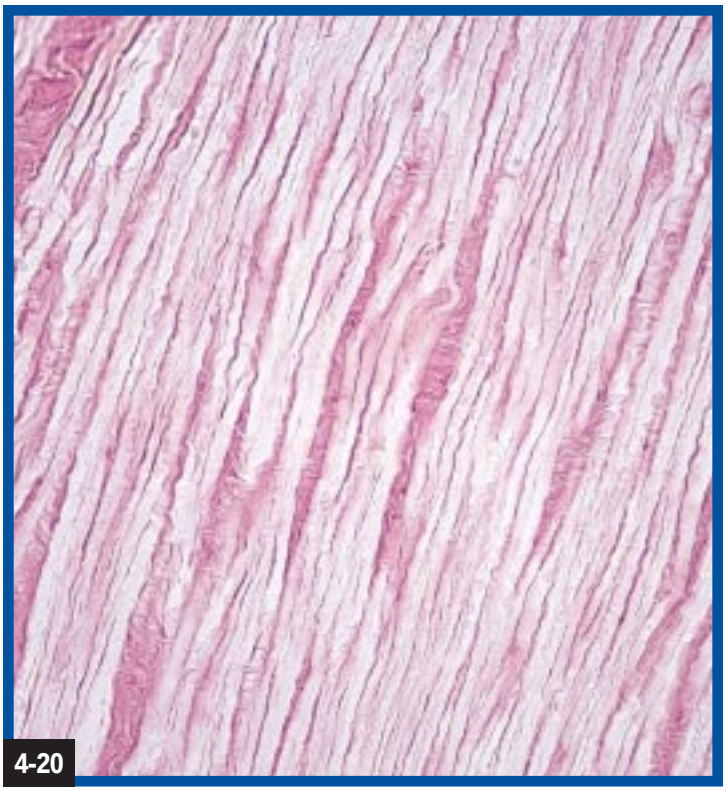
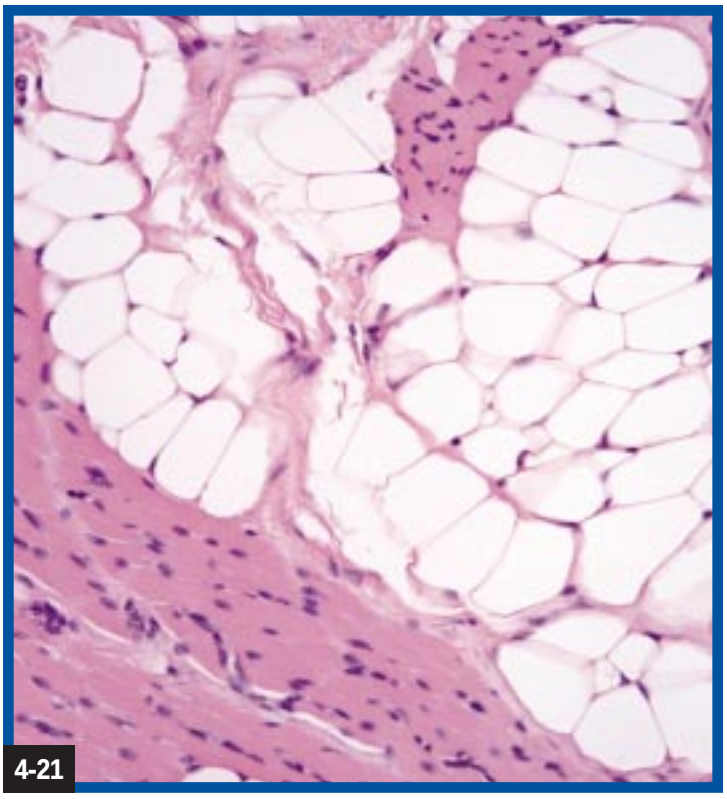
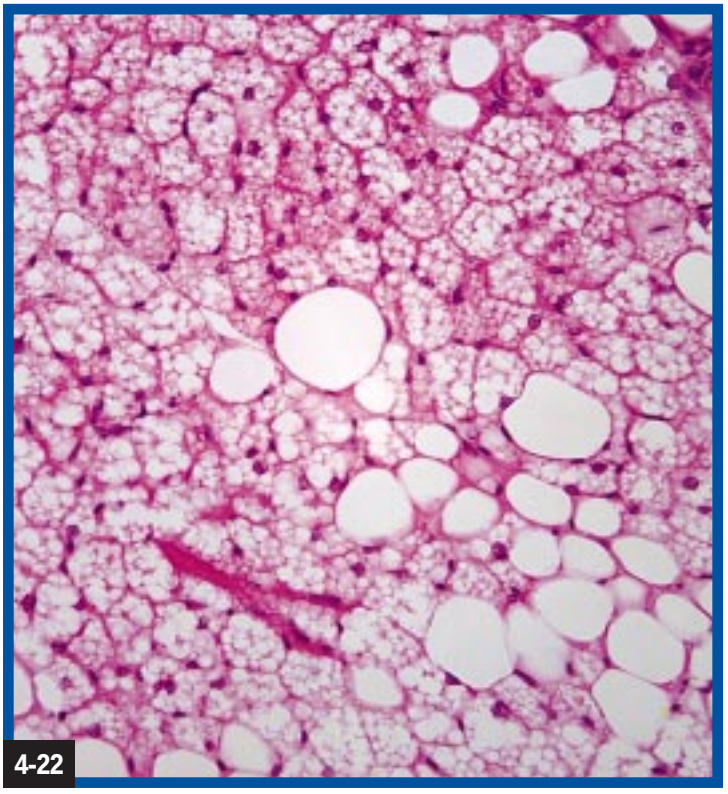


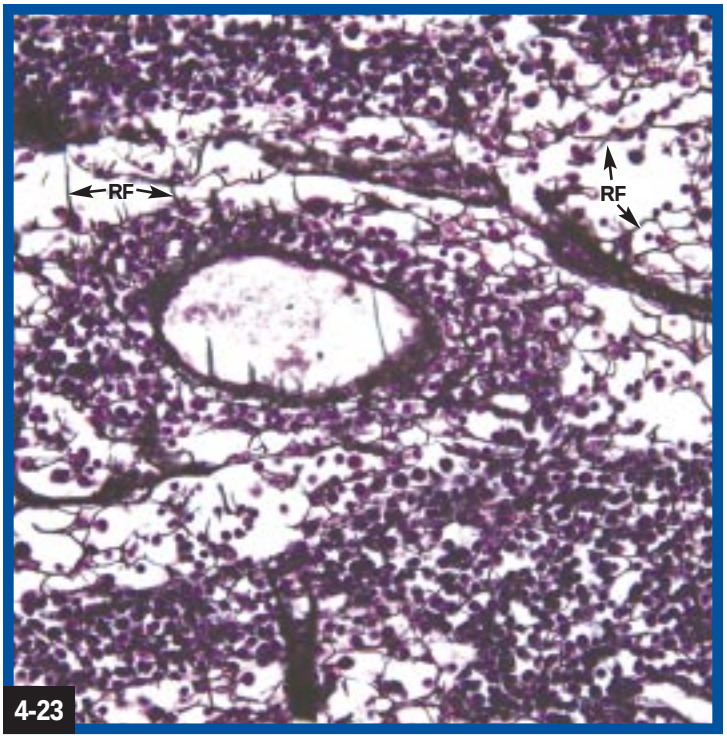
ELASTIC DENSE REGULAR CONNECTIVE TISSUE This specimen is an elastic ligament from the neck. The waviness of the fibers is an indication of their elasticity. *(X250)*



WHITE FAT White fat is made of unilocular adipocytes and may be found most anywhere loose connective tissue is found. This specimen is from a skeletal muscle, and the fat is filling in between the bundles of muscle fibers. *(X250)*



BROWN FAT Brown fat is made of multilocular adipocytes and in humans, is primarily found in the embryo. *(X250)*



RETICULAR CONNECTIVE TISSUE Lymphoid organs and bone marrow have a reticular connective tissue framework. This lymph node specimen was prepared with a silver stain so the reticular fibers (RF) could be seen. *(X250)*

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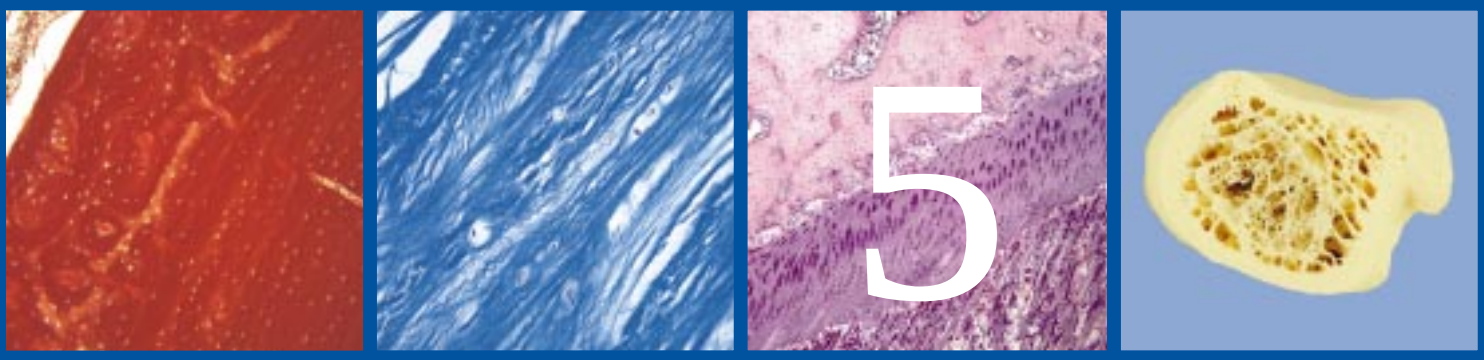
Cartilage and Bone

CHAPTER 5



Introduction to Skeletal Tissues

Cartilage and bone are specialized connective tissues with a firm to rigid matrix, suiting them for their skeletal and protective functions.

Basic Characteristics of Cartilage

Cartilage is on joint surfaces, forms the framework of the nose, ears, respiratory tree and part of the rib cage, and is located between vertebrae. It also comprises a majority of the embryonic skeletal system before it is replaced by bone. The semirigid matrix makes cartilage well-suited for these supporting functions.

Embryonically, cartilage begins developing from mesenchyme in chondrification centers. The mesenchymal cells differentiate into **chondroblasts**, which begin secreting matrix. When they become surrounded by matrix, they are called **chondrocytes** and the space each chondrocyte occupies is called a **lacuna** (Figure 5-1). When a chondrocyte grows and divides, it forms an **isogenous group** of cells in the lacuna. These cells continue producing matrix and become separated into different lacunae. The result is cartilage growth from the interior of the matrix, a process known as **interstitial growth**.

The characteristic consistency of the matrix is due to the grouped arrangement of proteoglycans and its degree of hydration. The matrix immediately around each lacuna is basophilic and is called **territorial matrix**; **interterritorial matrix** is found between lacunae (Figure 5-2). Collagen and elastic fibers are present in the matrix and confer strength and flexibility, respectively. Most of the time, collagen fibers are not easily seen in cartilage even though they are abundant. A silver stain (or other specialized elastin stain) must be used to visualize elastic fibers since H&E does not stain them.

Cartilage is avascular, but receives nourishment from blood vessels in the **perichondrium**, the fibrous membrane that surrounds most cartilage (Figure 5-3). It is composed of a superficial **fibrous layer** and a deeper **chondrogenic cell layer**. In **appositional growth**, the chondrogenic cells differentiate into chondroblasts that secrete new matrix on the cartilage's surface.

Types of Cartilage

There are three types of cartilage: hyaline cartilage, elastic cartilage, and fibrocartilage. **Hyaline cartilage** (Figures 5-1 through 5-4) is the most abundant of the three cartilage types. It is found in the nose and respiratory tree, on the sternal ends of the ribs, and on articular surfaces. It also forms the cartilage model of the skeleton during development. The matrix of hyaline cartilage is glassy in appearance (hence, "hyaline") and has collagen fibers in it, though they are not easily seen with the light microscope. Except in articular cartilage (Figure 5-5) a perichondrium is present.

Elastic cartilage (Figure 5-6) is found in the ears and epiglottis. It is very similar to hyaline cartilage, except that its matrix has numerous elastic fibers in addition to the collagen fibers. The chondrocytes also tend to be larger (at the expense of the matrix) and more numerous than in hyaline cartilage. A perichondrium is present.

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Fibrocartilage (Figure 5-7) is found in the intervertebral disks and the pubic symphysis. It has abundant collagen fibers in the matrix and the chondrocytes tend to be seen in rows parallel to the fiber bundles. There is no perichondrium.

Basic Characteristics of Bone—Matrix and Cells

Bone matrix is composed of about 25% organic (Type I collagen) and 65% inorganic (calcium hydroxyapatite crystals) materials, with most of the remainder being water. The collagen provides some flexibility and tensile strength to the bone, whereas the inorganic materials confer hardness. There are four major cells of bone tissue. These are osteoprogenitor cells, osteoblasts, osteocytes, and osteoclasts.

Osteoprogenitor cells (Figure 5-8) are derived from mesenchymal cells and have the ability to differentiate into osteoblasts, and under some circumstances, into chondrogenic cells. They are elongated cells and are found associated with periosteum and endosteum (see below).

Osteoblasts (Figure 5-8) develop from osteoprogenitor cells and are therefore also found lining external and internal bone surfaces, but they have more of a cuboidal shape. Osteoblasts are actively involved in secreting collagen-rich **osteoid**, the precursor to true bone matrix during bone growth, repair and remodeling. Osteoid is subsequently calcified to make the bony matrix.

Osteocytes (Figure 5-8) are osteoblasts that have become surrounded by matrix. They occupy **lacunae** in the matrix and are responsible for maintaining matrix composition.

Osteoclasts (Figures 5-8 and 5-9) are large, multinucleate cells responsible for bone resorption; that is, they destroy bony matrix. They are often found associated with a pit in the bone called a **Howship's lacuna**. Osteoclasts are active during the growth, repair, and remodeling processes. Their activities are balanced with those of osteoblasts so that (normally) bone mass remains constant.

Membranes of Bone

Bone surfaces are lined with one of two fibrous membranes: periosteum or endosteum. **Periosteum** (Figure 5-10) is the fibrous membrane that surrounds bone. Like its counterpart in cartilage, periosteum has a superficial **fibrous layer** and a deeper **cellular layer**. The cellular layer has osteoprogenitor cells that have the ability to become bone-forming cells. Periosteum is attached to bone by **Sharpey's fibers**, collagen bundles that penetrate the bone matrix (Figure 5-11). All internal surfaces are lined with a reticular connective tissue called **endosteum**, which is also associated with osteoprogenitor cells (Figure 5-12).

Types of Bone Tissue

Bone tissue is of two types: spongy (cancellous) bone and compact bone (Figure 5-13). Both types are in all bones, but their relative amounts differ depending on the particular bone and the specific part of the bone.

Compact bone has a dense bony matrix with canals that carry blood vessels. **Volkmann's canals** penetrate from the surface and **Haversian canals** run more or less parallel to the surface (Figure 5-14). The structural and functional unit of compact bone is the **Haversian system** or **osteon** (Figure 5-15). Each Haversian system consists of a central Haversian canal with its neurovascular bundle. The bony matrix is arranged in concentric rings around the canal **(concentric lamellae)** with osteocytes occupying lacunae at their junctions. Osteocytes maintain contact with other osteocytes by way of cellular processes that pass through tiny **canaliculi**. In this fashion, nutrients and oxygen from the blood vessel can diffuse from cell to cell outward toward the periphery of the Haversian system. A calcified cement line encircles the outer margin of the Haversian system.

Spongy bone (Figure 5-16) is found in the interior of bones. It is made of a delicate network of bony **trabeculae** that are arranged to strengthen the bone according to the mechanical loads placed on it. Irregular arrangements of lamellae are present, but Haversian systems are not.

Bone Growth

There are two basic mechanisms of bone growth. In in**tramembranous ossification**, bone forms within a mesenchymal membrane. In **endochondral ossification**, bone tissue replaces a hyaline cartilage model. In both mechanisms, bone is initially formed as spongy bone.

Intramembranous ossification (Figure 5-17) is responsible for producing the flat bones of the skull. The process is relatively straightforward.

1. Mesenchymal cells differentiate into osteoblasts at the **primary center of ossification** and begin depositing bony matrix to form trabeculae of spongy bone.
2. Ossification continues radially from the ossification center, like ripples spreading from dropping something in water.
3. Bone marrow develops in the spaces between trabeculae.
4. Periosteum and endosteum develop from the unossified mesenchyme membrane.
5. The surfaces are remodeled to form compact bone. In the skull, these layers are called **inner** and **outer tables**. The spongy bone between them is the **diploë**.

Endochondral ossification is involved in producing most bones of the skeleton, and is most easily understood by studying appendicular long bones. While studying this process, it is important to remember that the cartilagenous model grows in length and diameter even as parts of it are being replaced by bone. (After all, the skeleton must be functional and an appropriate size at all times during

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embryonic growth.) Endochondral ossification is outlined in Figure 5-18 and can be summarized by the following steps:

1. Hyaline cartilage occupies the **zone of reserve cartilage** and acts as a source of cartilage to undergo the process described below.
2. Normal chondrocytes multiply in the **zone of proliferation (multiplication)**.
3. The chondrocytes enlarge (hypertrophy) in the **zone of hypertrophy**.
4. The cartilage matrix calcifies in the **zone of calcification**.
5. Chondrocytes deteriorate and bone is deposited on the remaining fragments of calcified matrix in the **zone of ossification**.
6. Osteoclasts remove the newly formed bone to make the marrow cavity in the **zone of erosion**.

Examine the photomicrographs in Figures 5-19 to 5-25 as you read the details of this process.

1. Endochondral ossification begins with a bone made of hyaline cartilage. A **primary center of ossification** (Figure 5-19a) appears at the center of the shaft (diaphysis). This is evidenced by the chondrocytes of the region multiplying and enlarging at the expense of the matrix. What matrix is left becomes calcified and appears more basophilic. Since the calcified matrix retards diffusion of oxygen and nutrients, chondrocytes begin to deteriorate within the enlarged lacunae.
2. Simultaneous with the activities of the primary ossification center, osteoblasts develop deep to the perichondrium of the shaft and deposit a ring of periosteal bone called a **bony collar** (Figure 5-19a). The bony collar acts as a splint to support the bone as the internal cartilage is eroded away. The perichondrium develops into a periosteum.
3. Blood vessels **(periosteal buds)** grow into the enlarged lacunae and form primary marrow spaces (Figures 5-19b and 5-19c). They bring osteoprogenitor cells into the region, some of which become osteoblasts that deposit osteoid and then bone on the remaining cartilagenous fragments.
4. After a region has ossified, osteoclasts move in and resorb the bone to form the marrow cavity (Figures 5-19d and 5-19e). This will not occur during endochondral ossification of short or irregular bones that lack a marrow cavity.
5. The process of bone replacing cartilage spreads toward the ends of the bones (epiphyses), following the same sequence of events as occurred in the primary center: enlargement and multiplication of chondrocytes, calcification of matrix, deterioration of chondrocytes, and deposition of bone (Figures 5-20 and 5-21).
6. Growth in diameter occurs as **periosteal bone** is deposited on the surface while osteoclast activity removes bone from the marrow cavity side of the diaphysis (Figure 5-22).
7. All bone tissue initially forms as spongy bone, so it must be remodeled on the surface to become compact bone. The process involves deposition of the lamellae from outermost to innermost around the neurovascular bundle, which ends up in the remaining space, the Haversian canal (Figure 5-23).
8. At about the time of birth, **secondary centers of ossification** appear in one or both ends (epiphyses) of the long bone (Figure 5-24). These ossify the epiphyses leaving cartilage in two places: on the surface of the epiphysis as **articular cartilage**, and in the **epiphyseal plate** that joins the epiphysis with the diaphysis (Figure 5-25). The epiphyseal plate continues to produce new cartilage on its epiphyseal side at the same rate it is being replaced by bone on the diaphyseal side. In this fashion, the plate remains the same thickness, but appears to grow away from the center of the bone. This results in longitudinal growth of the bone. At some time during development (typical for each bone), the epiphyseal plate ossifies and longitudinal growth is completed.

Synovial Articulations

Synovial joints (Figure 5-26) are characterized by having a **synovial (joint) cavity**. This makes them freely moveable. Lining the bones' surfaces is **articular cartilage**. It is made of hyaline cartilage (from the original cartilage model that remained unossified) without a perichondrium. Lining the cavity is a vascular and fibrous **synovial membrane** that secretes a lubricating **synovial fluid** (Figure 5-27). Strengthening the joint from the outside is a fibrous **joint capsule** that is continuous with the periosteum of the articulating bones. The capsule may contain thickenings that act as **ligaments**, or the ligaments may be separate from the capsule. Other cartilages (generally fibrocartilage) may be associated with the interior of the joint. The **menisci** of the knee joint are an example.

Muscular Attachments to Bone

Skeletal muscles either attach to bone directly or by way of a tendon. In the first instance, the muscle fibers extend to the periosteum and the connective tissue components of the muscle blend in with the connective tissue fibers of the periosteum (Figure 5-28). The periosteum itself is attached to the bone by Sharpey's fibers, and these are especially substantial at the point of muscular attachment. If the muscle attaches by way of a tendon, then it is the tendon fibers that mix with the periosteal fibers.

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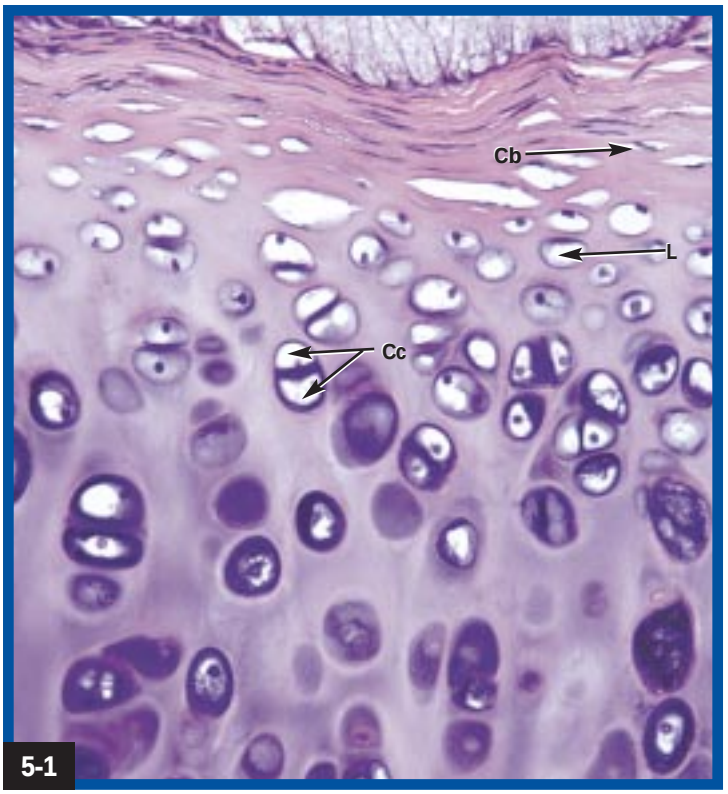
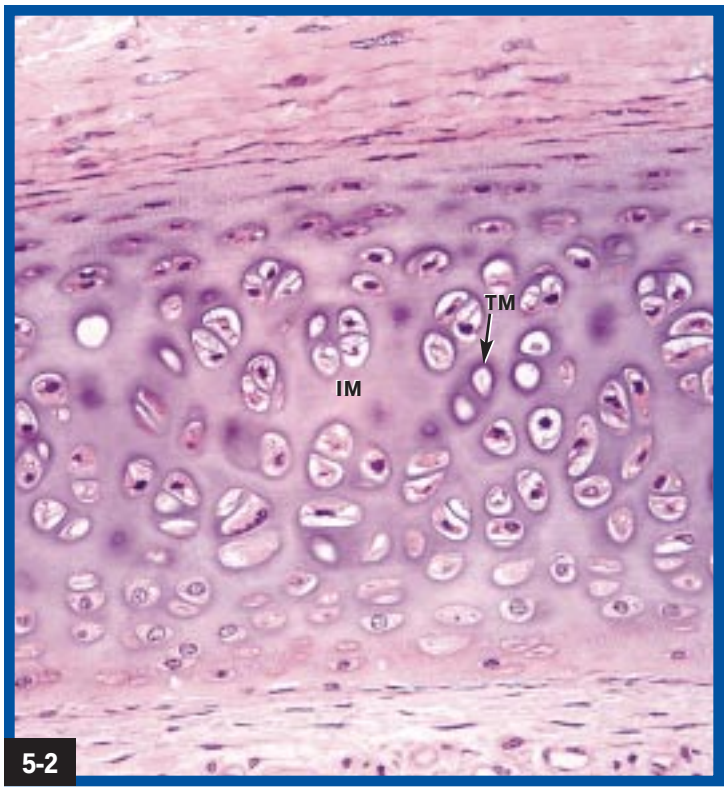
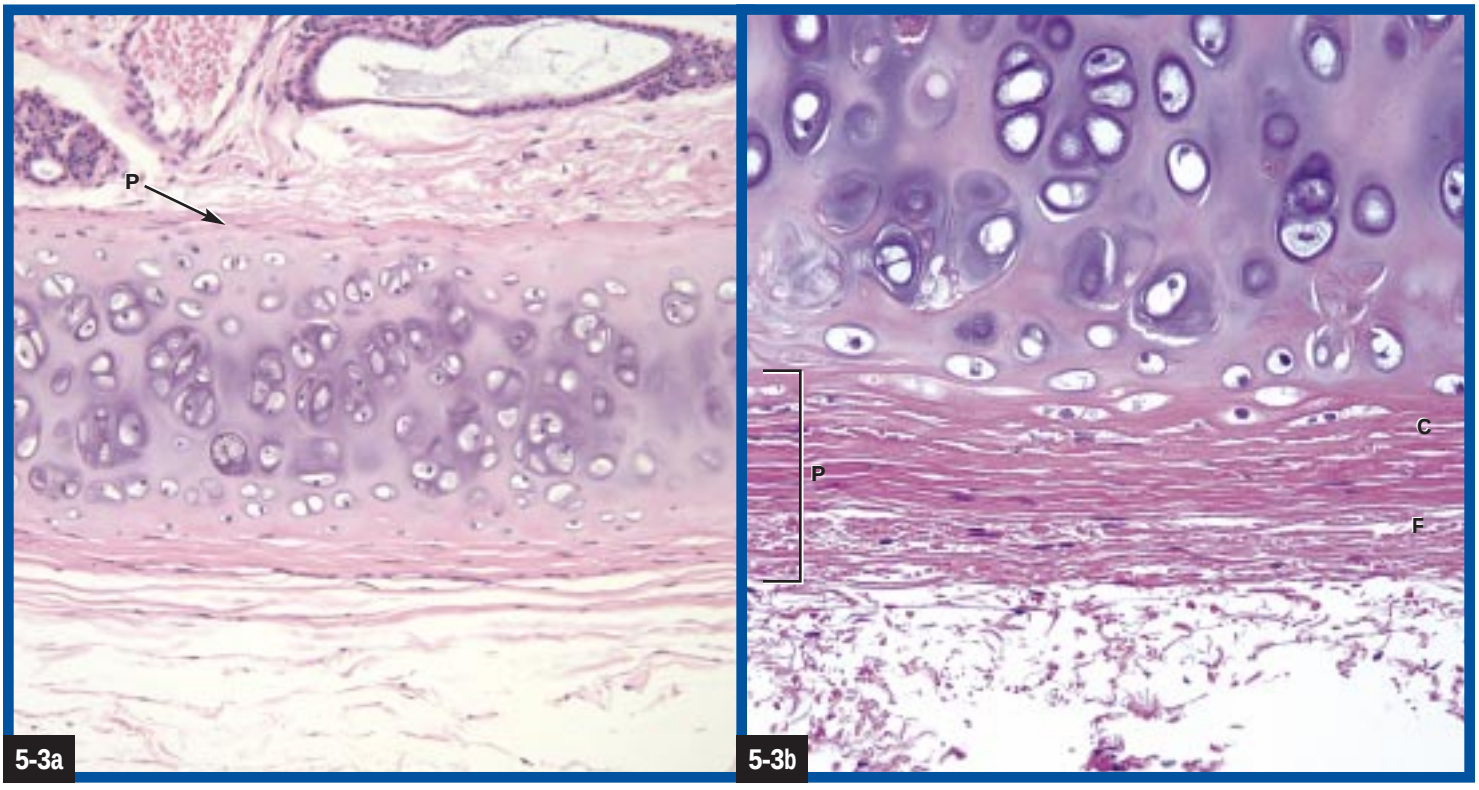


THE CELLS OF CARTILAGE Chondroblasts (Cb), isogenous groups of chondrocytes (Cc), and some empty lacunae (L) (artifacts of preparation) are visible in this micrograph of hyaline cartilage. *(X250)*



CARTILAGE MATRIX Territorial matrix (TM) around the chondrocytes stains darker than the interterritorial matrix (IM) between lacunae. This specimen is hyaline cartilage. *(X250)*



PERICHONDRIUM The vascular fibrous membrane around cartilage is called perichondrium (P). (a) The pink layer is the perichondrium surrounding hyaline cartilage. The distinction between the outer fibrous layer and inner chondrogenic layer is not sharp. (*X125*) (b) This hyaline cartilage specimen has a thicker perichondrium. The outer fibrous (F) and inner chondrogenic (C) layers are visible, but still are not sharply separated. *(X125)*

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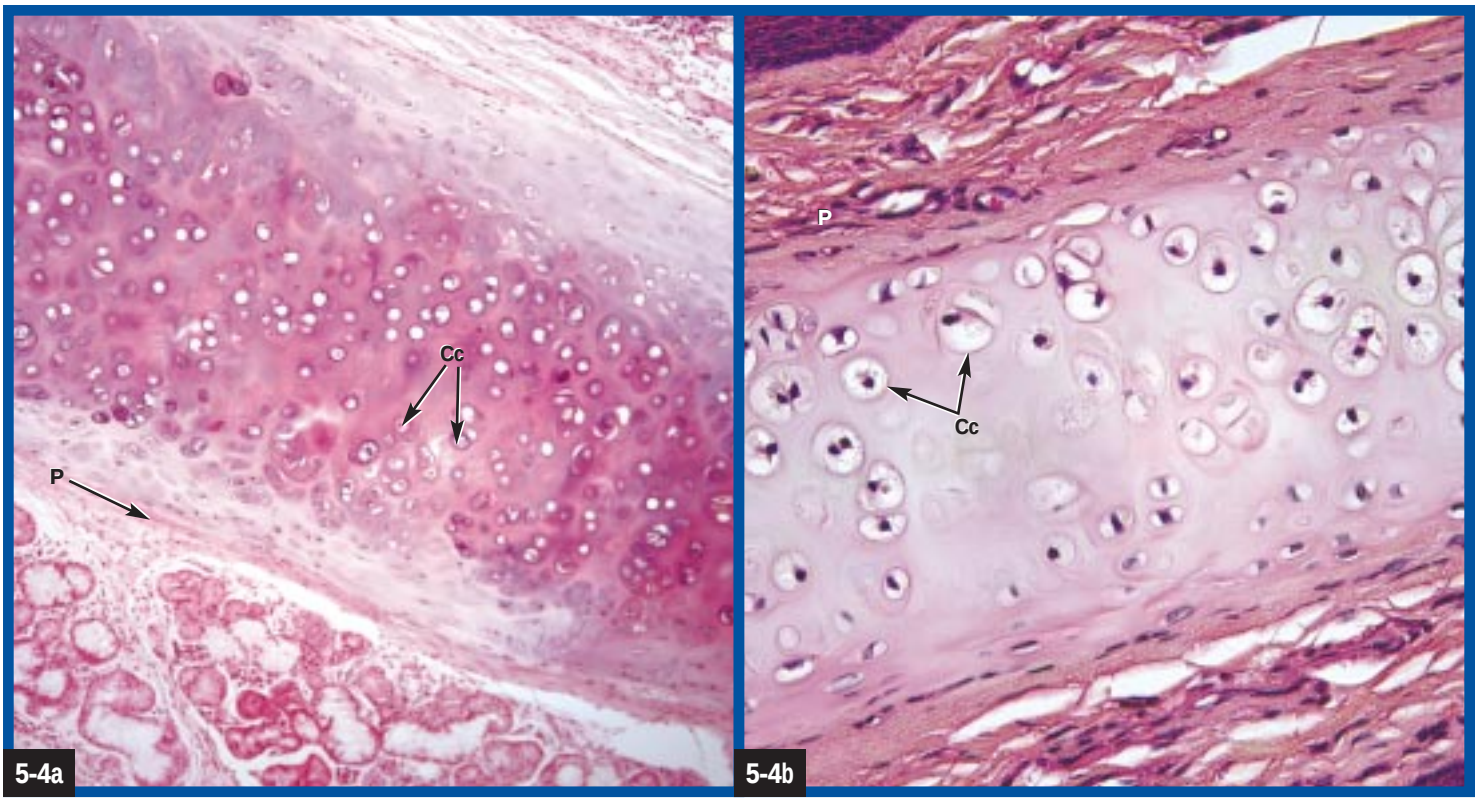
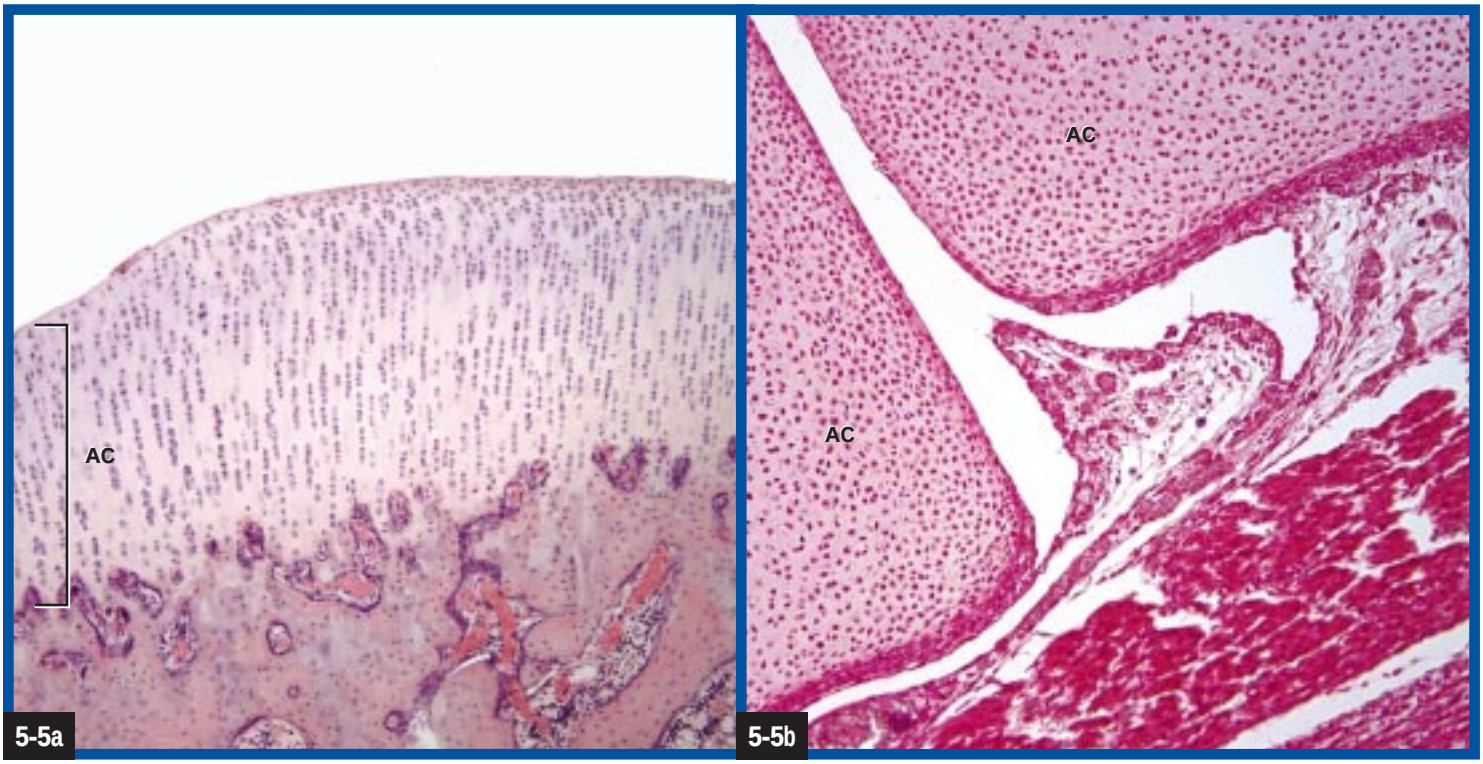


HYALINE CARTILAGE The most common form of cartilage is hyaline cartilage. Its matrix presents a smooth appearance even though collagen fibers are present. Perichondrium (P) and chondrocytes (Cc) are visible in both specimens. Specimen (a) is from the trachea. (*X65*) Specimen (b) is a section of the nasal septum. *(X250)*



ARTICULAR CARTILAGE The hyaline cartilage covering joint surfaces lacks a perichondrium. (a) This bone has been removed from its joint during preparation, but the articular cartilage (AC) on its joint surface is apparent. (*X65*) (b) This micrograph shows two articulating bones with their articular cartilages. *(X65)*

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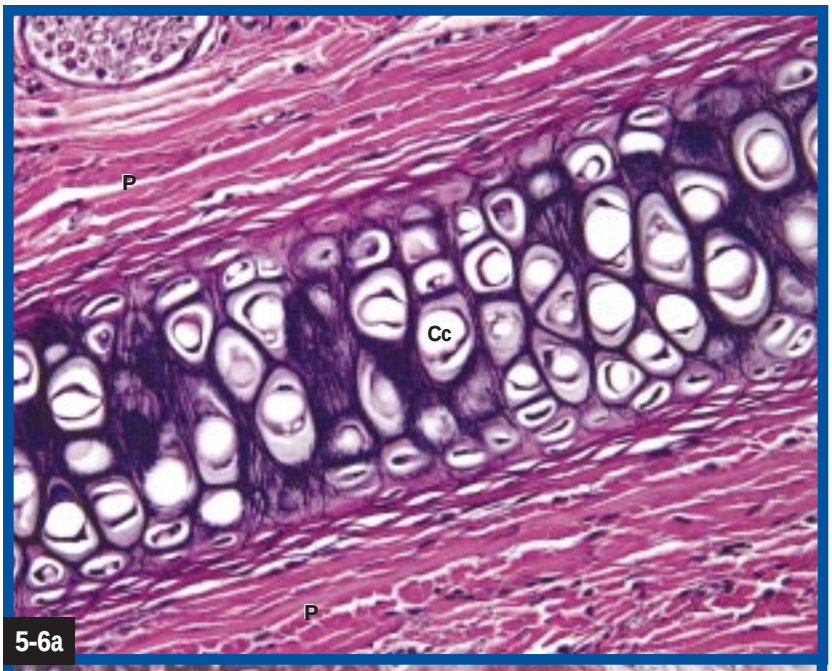

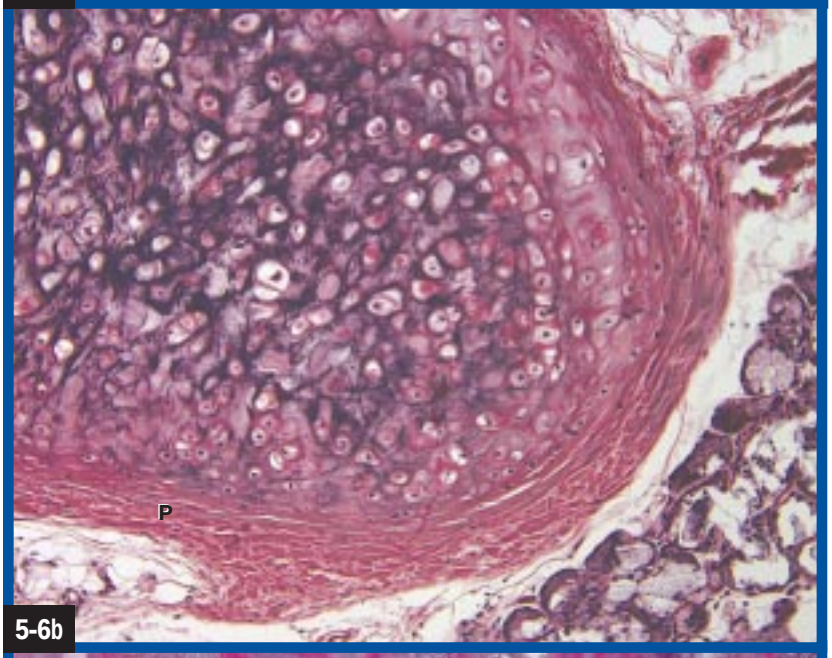

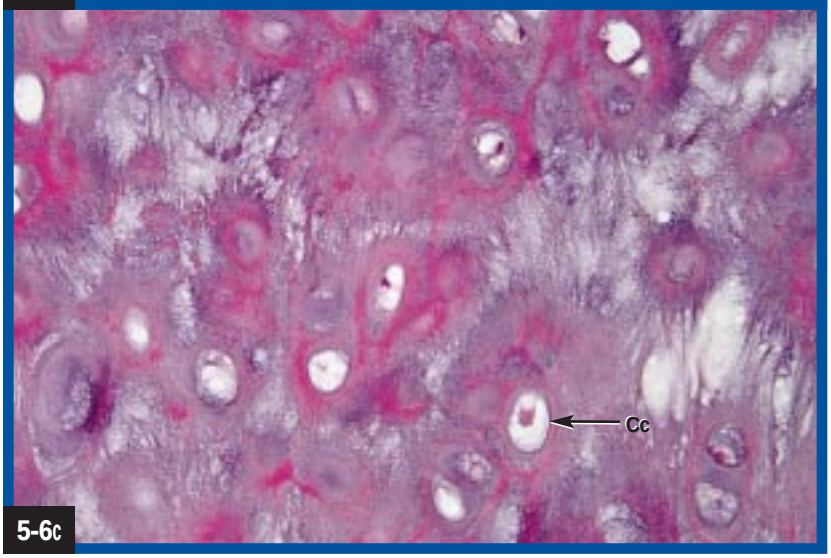

ELASTIC CARTILAGE The framework of the ear and epiglottis is made of elastic cartilage. A silver stain was used to highlight the elastic fibers in the top two specimens. Notice the perichondrium (P) and relatively large chondrocytes (Cc). Specimen (a) is from the external ear. (*X210*) Specimens (b) and (c) are from the epiglottis (X100 and X210, respectively).

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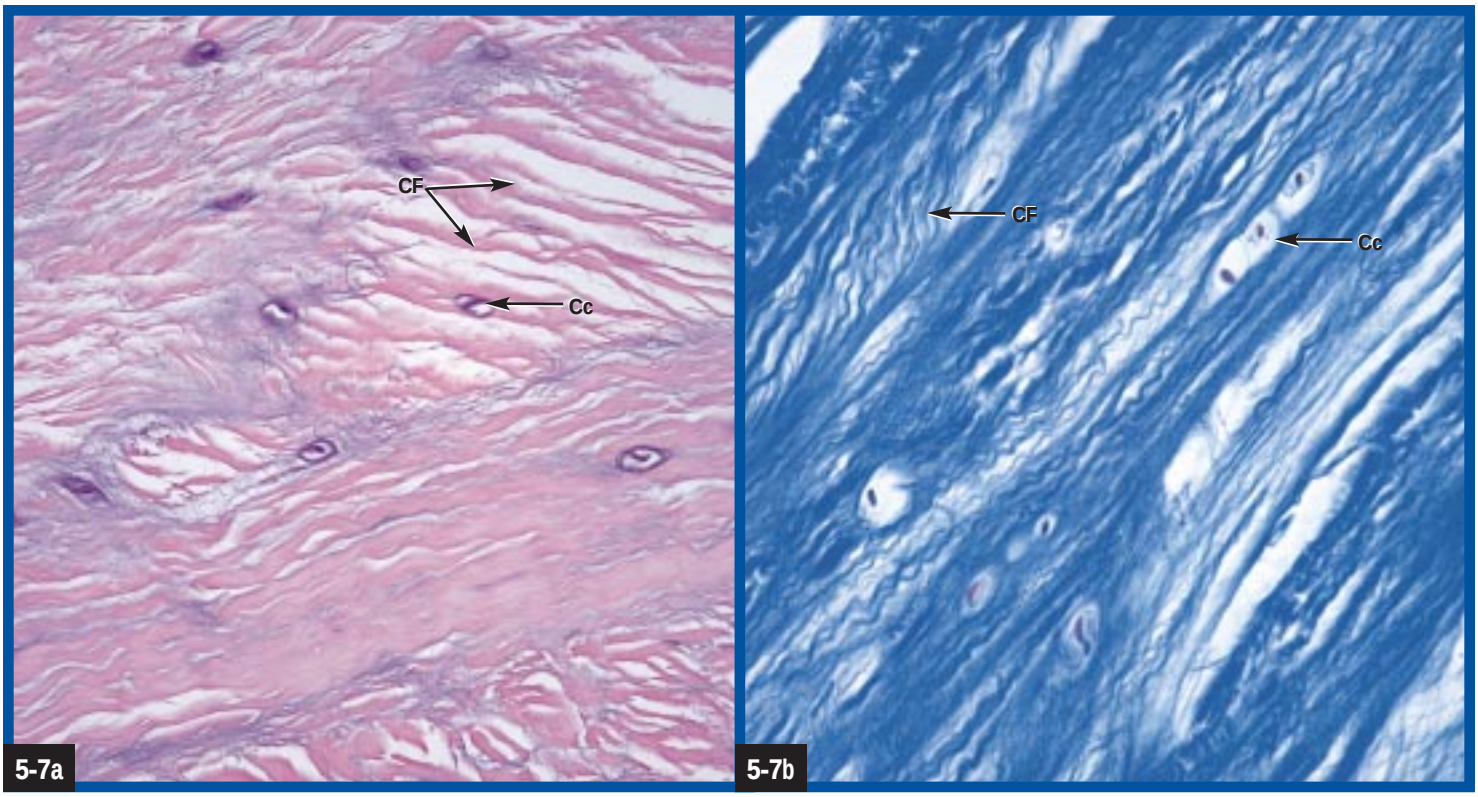
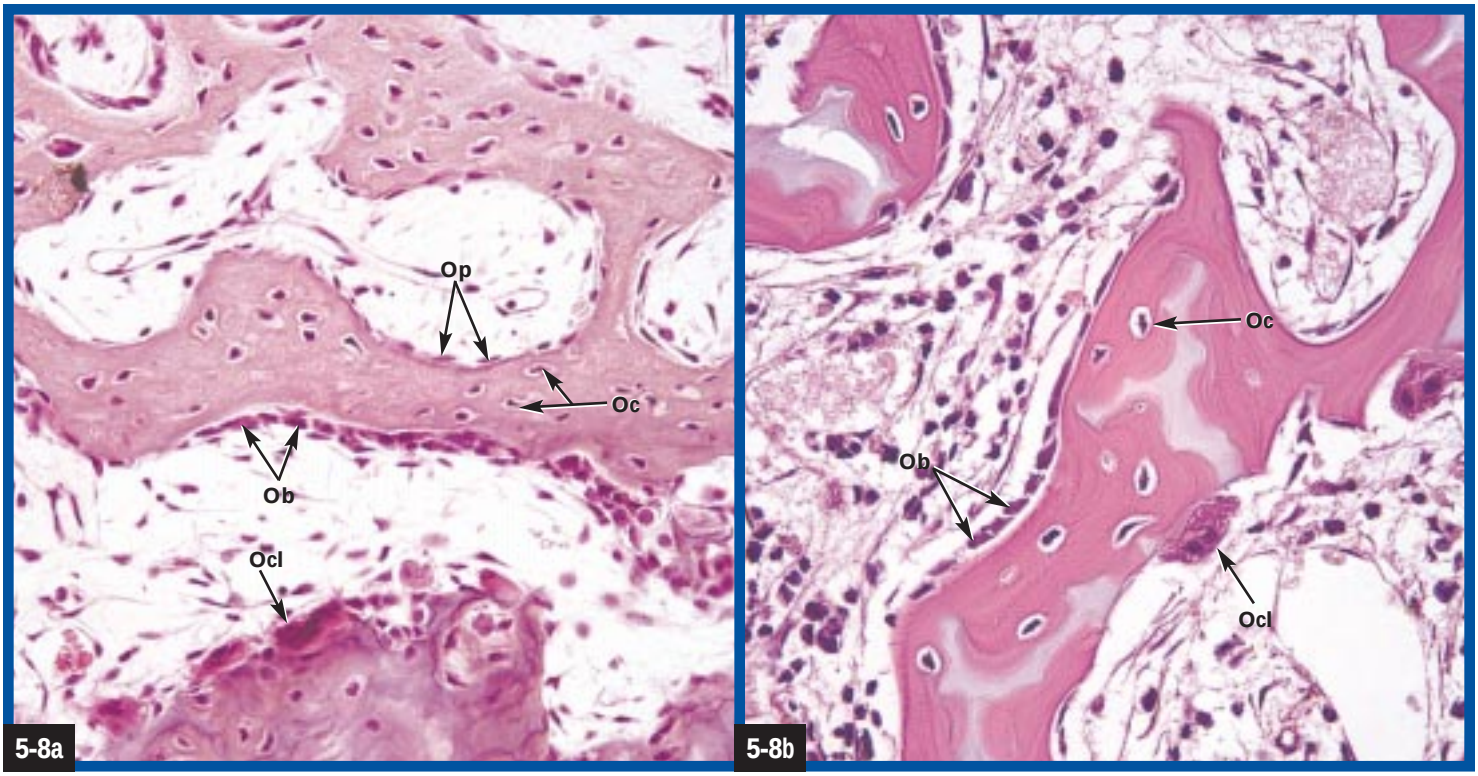


FIBROCARTILAGE Intervertebral disks and the pubic symphysis are made of fibrocartilage. It is characterized by dense bundles of collagen fibers (CF) in its matrix and the absence of a perichondrium. Often the chondrocytes (Cc) occur in lines, as in (b). Both specimens are from intervertebral disks and were magnified. *(X130)*



BONE CELLS These two micrographs show the four types of bone cells. Osteoprogenitor cells (Op) and osteoblasts (Ob) are found in rows on the surface of bone, associated either with endosteum or periosteum. Osteoprogenitor cells are flatter than osteoblasts. Osteocytes (Oc) are cells of mature bone and are encased by the bony matrix. Osteoclasts (Ocl) are large, multinucleate cells found on the surface of bone. Micrograph (a) was magnified X250. Micrograph (b) was magnified X380.

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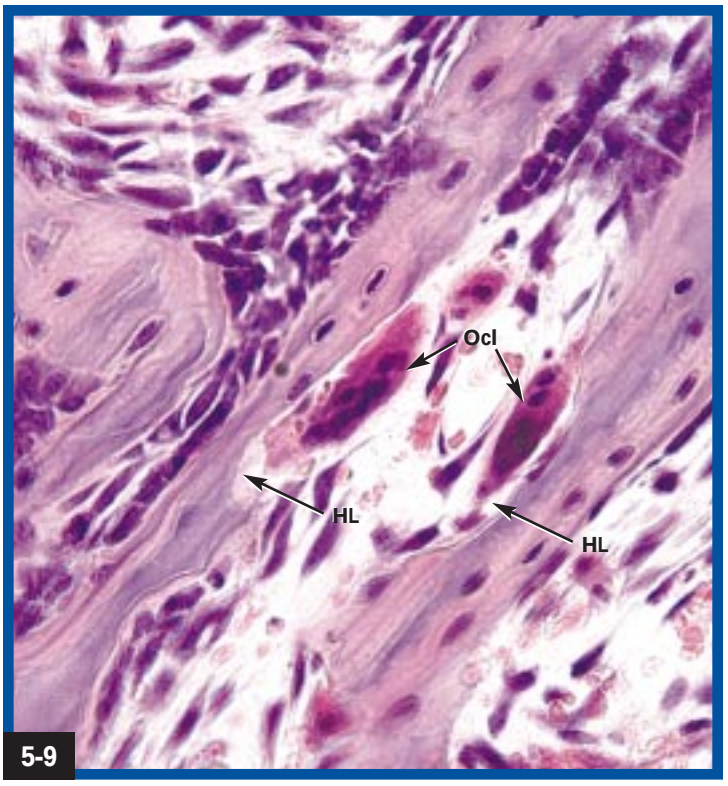
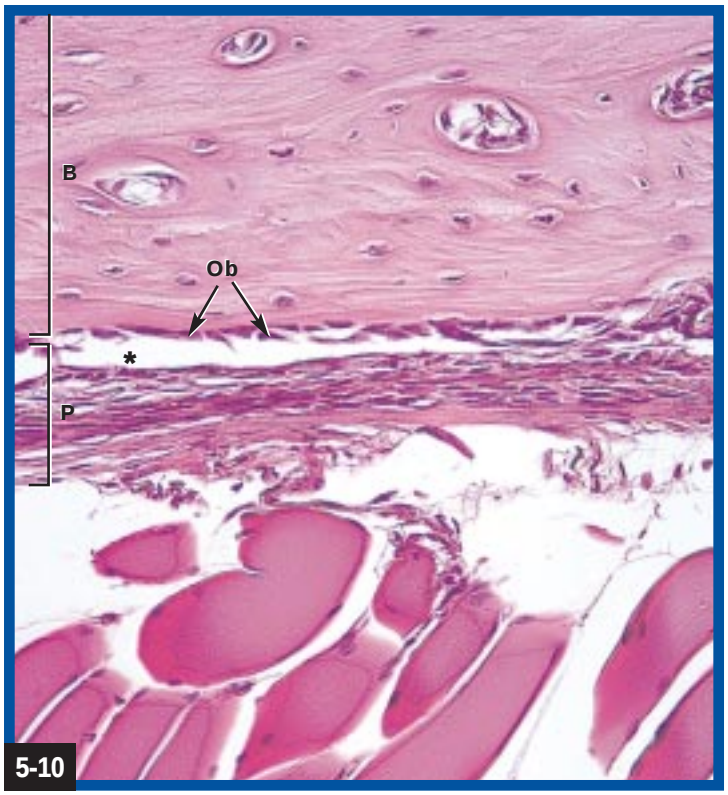
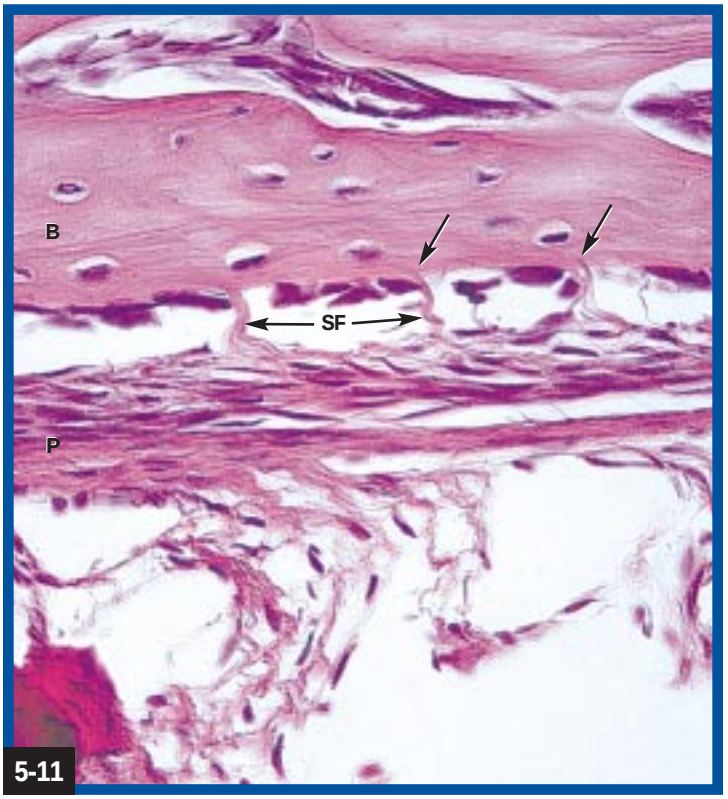


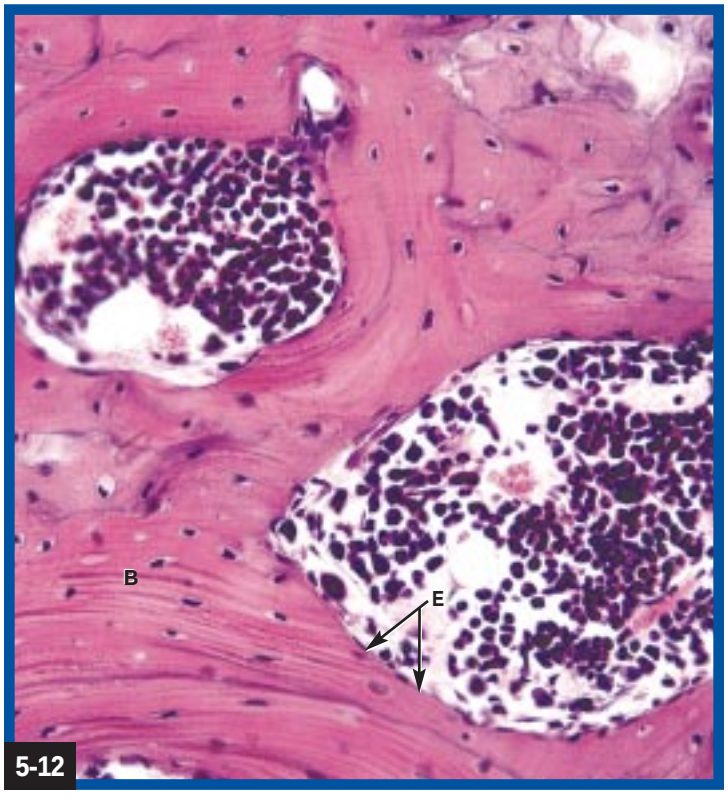
OSTEOCLASTS Bone is resorbed by multinucleate osteoclasts (Ocl). They often erode a pit in the surface of the bone called a Howship's lacuna (HL). *(X380)*



PERIOSTEUM Periosteum (P) is the fibrous membrane around bone (B). It has an outer fibrous layer and an inner osteogenic layer with osteoprogenitor or osteoblast (Ob) cells. In this specimen, the space (*) is an artifact of preparation. *(X250)*



SHARPEY'S FIBERS Periosteum (P) is anchored to the bone (B) by collagen bundles called Sharpey's fibers (SF). In this micrograph, they can be seen to penetrate the bony matrix (arrows). *(X380)*



ENDOSTEUM All inner surfaces of bone (B) are lined with a delicate connective tissue called endosteum (E). In this specimen, the endosteum is associated with osteoprogenitor cells. *(X250)*

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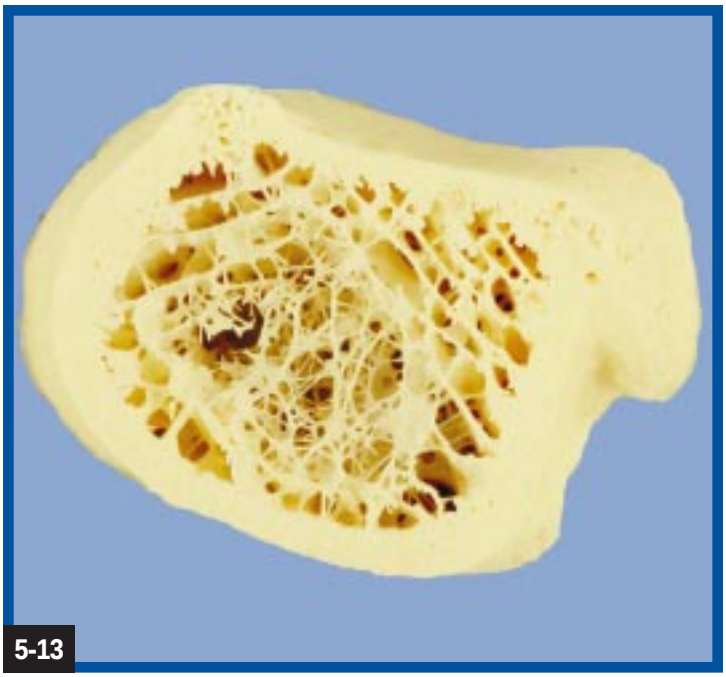
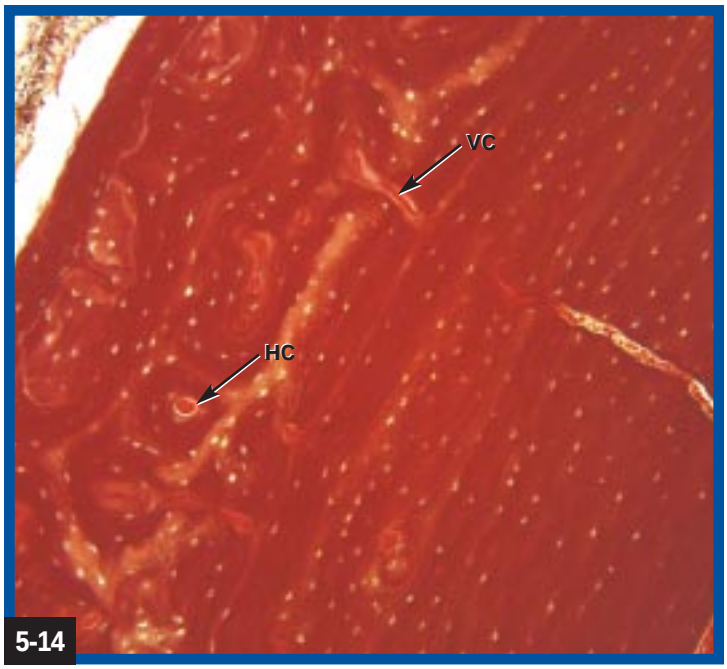
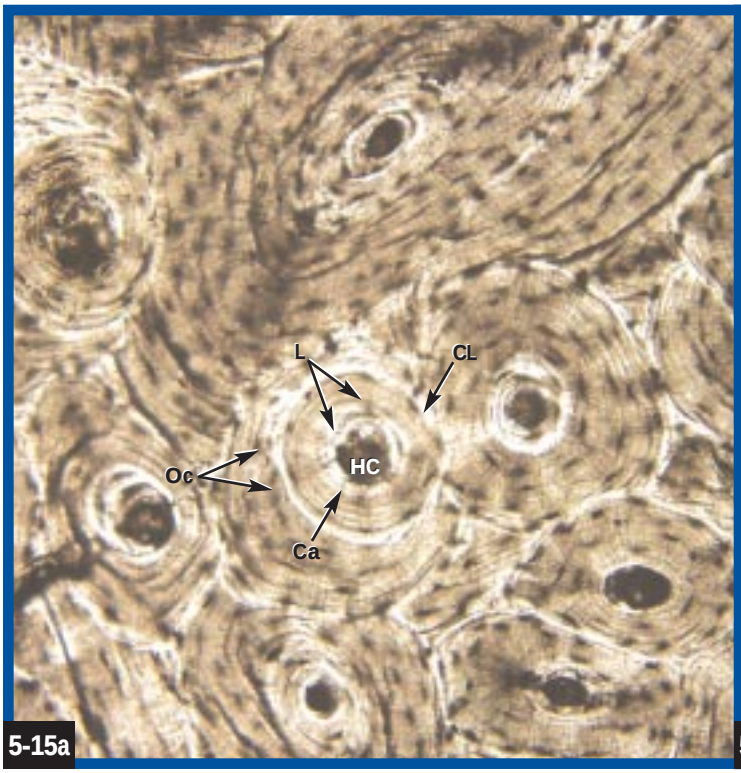

5-13

TYPES OF BONE TISSUE Dense, compact bone covers outer surfaces, whereas the interior of a bone is composed of more delicate spongy bone tissue. Both types are found in all bones, but in different proportions. (Photograph by Gary D. Wisehart)

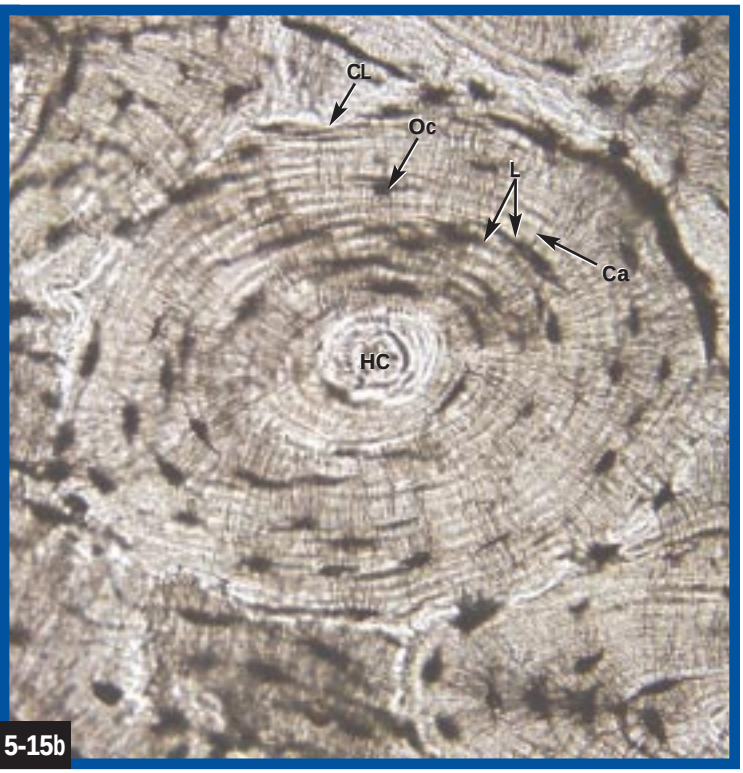


5-14

THE CANALS OF COMPACT BONE The blood vessels of compact bone travel through canals. Volkmann's canals (VC) carry vessels from the surface to the interior. Haversian canals (HC) transmit blood vessels parallel to the surface. In this decalcified bone specimen cut in cross section, the Volkmann's canals are cut longitudinally or obliquely, whereas the Haversian canals are cut in cross section. Osteocytes are barely visible as white specks in the matrix. *(X100)*



5-15a



5-15b

COMPACT BONE IN CROSS SECTION (GROUND BONE PREPARATION) Due to the hardness of compact bone matrix, these specimens were not sectioned with a microtome, but instead were ground down to their final thickness. The osteocytes and blood vessels often are absent from preparations such as these. The central Haversian canals (HC), concentric lamellae (L), osteocytes (or at least their lacunae) (Oc), canaliculi (Ca), and cement lines (CL) are visible in both specimens. *(X100)*

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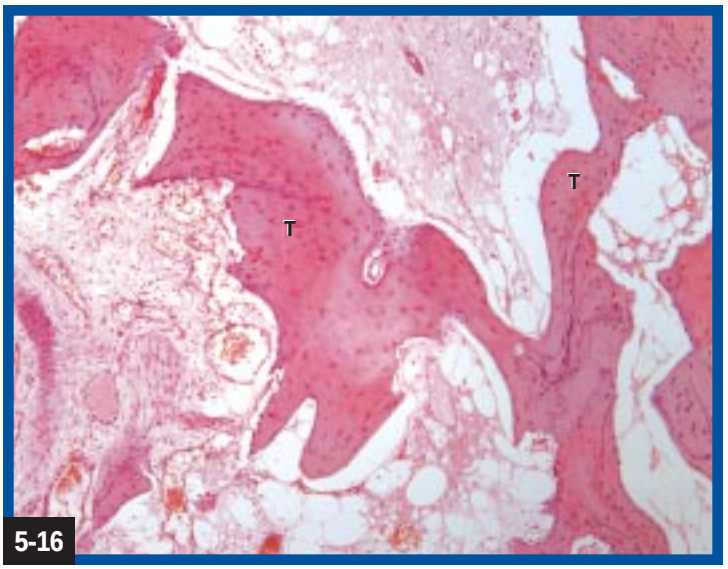
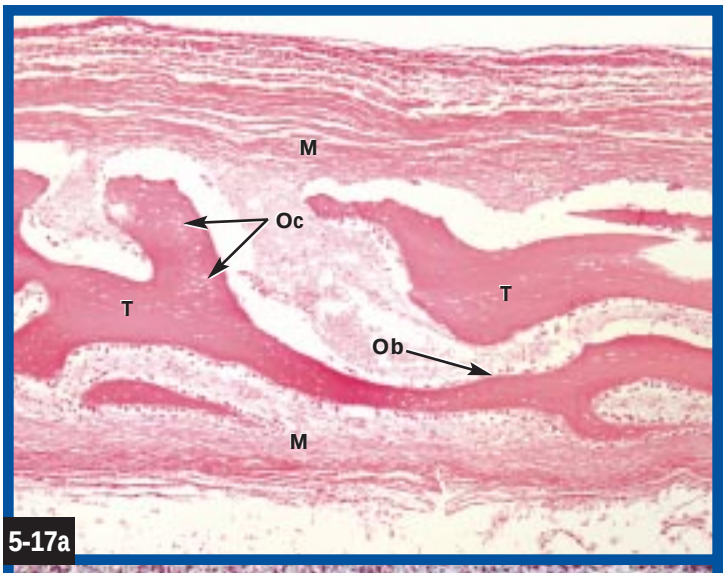
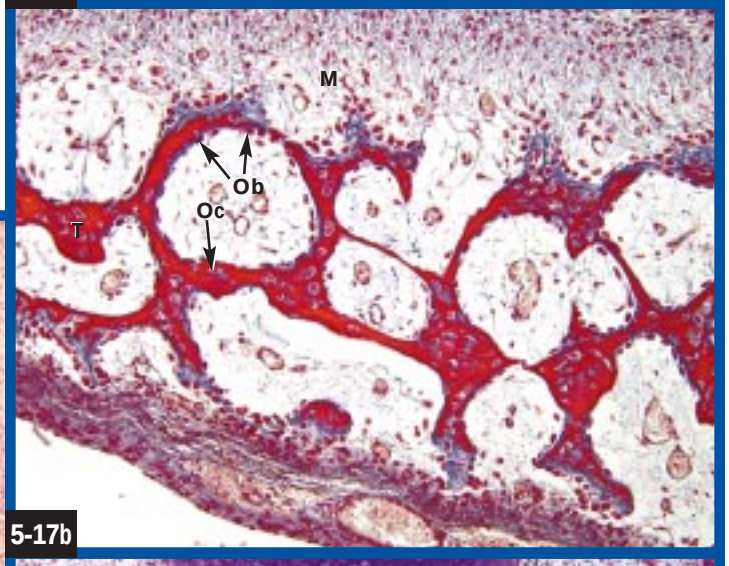
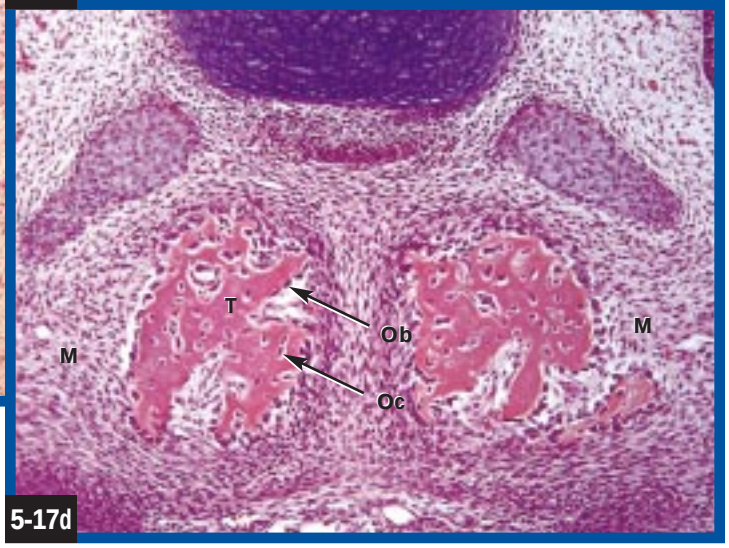


SPONGY BONE Trabeculae (T) of spongy bone contain osteocytes and lamellae of bone, but these are not organized into Haversian systems. *(X50)*







INTRAMEMBRANOUS OSSIFICATION Intramembranous ossification occurs within a mesenchymal membrane. Trabeculae of bone (T), osteoblasts (Ob), and osteocytes (Oc) are identifiable, as is the membrane (M) in each specimen. (a) This is a fairly advanced specimen from the skull. The outer and inner surfaces will be remodeled into compact bone called the inner and outer tables. The internal spongy bone will be called diploë. (*X50*) (b) This membrane bone also has yet to produce the surface compact bone, but the trabeculae are well-formed. (*X100*) (c) This specimen is from a section of the entire skull of an embryonic vertebrate. The membrane bone is orange-red and has the characteristic osteoblasts on its surface and the trapped osteocytes within. The white space at the left is part of the nasal cavity, and the purple curled structure is hyaline cartilage (HC) of a nasal concha. (*X50*) (d) This is a frontal section of an embryonic skull. The centers of ossification and membrane are visible. Notice the osteoblasts on the surface that are partially surrounded by bone. The hyaline cartilage of the nasal septum is the blue object at the center top. *(X100)*

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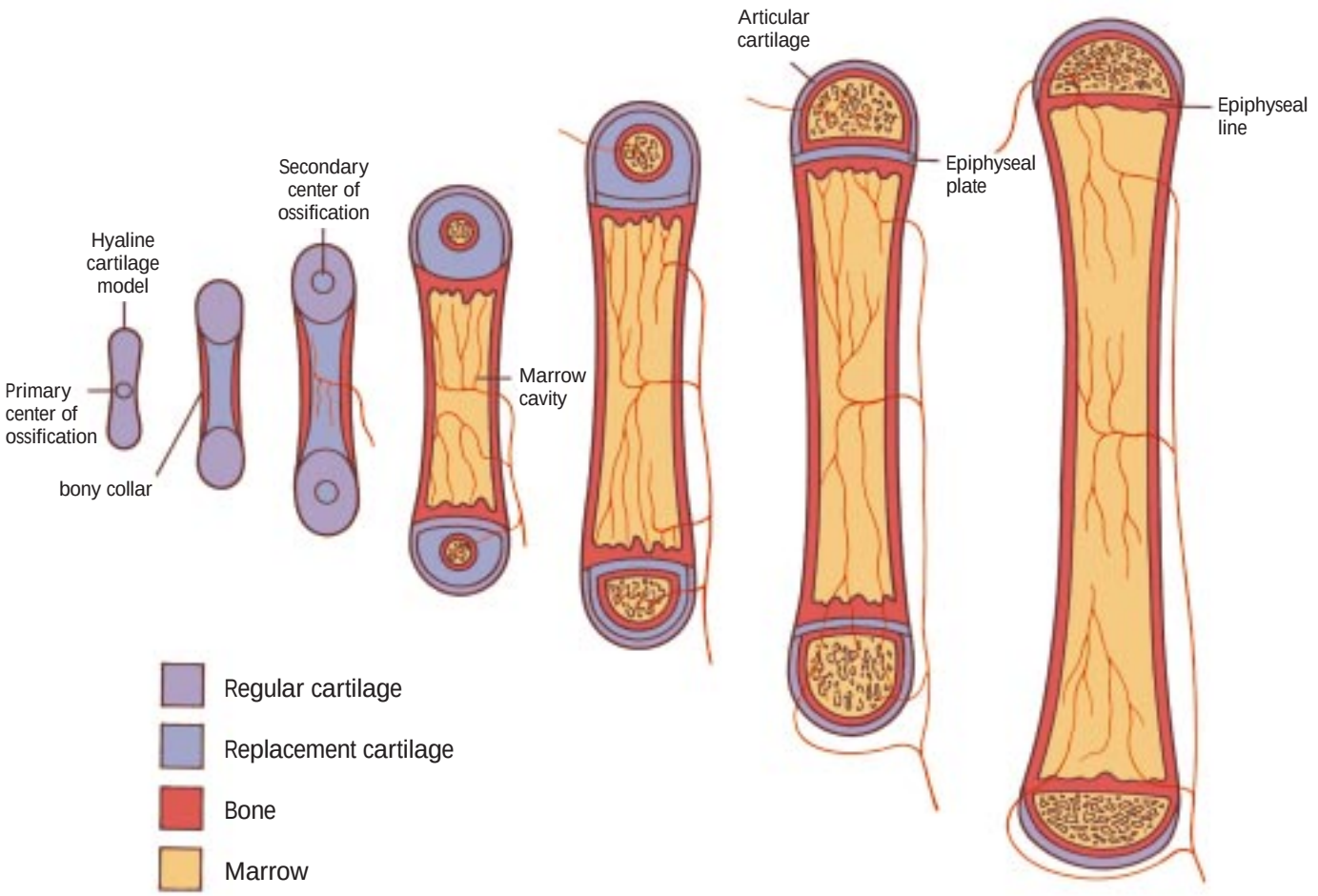

5-18

ENDOCHONDRAL OSSIFICATION IN A LONG BONE This complex process starts with a hyaline cartilage model of the bone. The cartilage is replaced by bone tissue as the bone grows in size. See page 47 for details.

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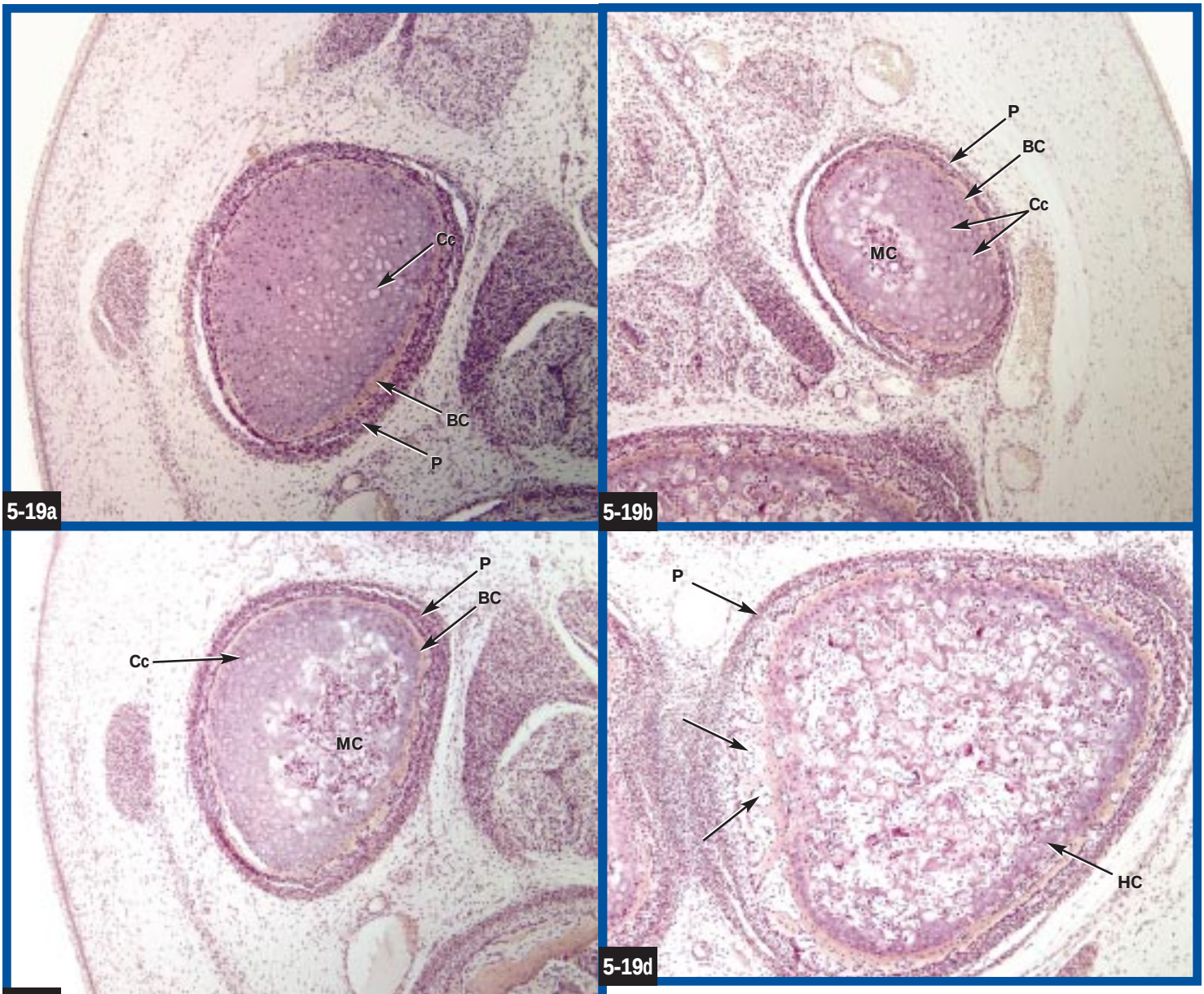

Endochondral Ossification at the Primary Center Shown in Cross Section While they are from different bones, this collection of images should allow the reader to piece together the dynamic process of endochondral ossification. All images were magnified X50. (a) The primary center of ossification has become active, as evidenced by the enlarged chondrocytes (Cc) at the center and the pink bony collar (BC) produced by subperiosteal osteoblasts. The periosteum (P) is also visible. Notice that the hyaline cartilage at the periphery still looks like typical hyaline cartilage. (b) The chondrocytes and matrix in the bone's center have begun to break down and osteoblasts and other marrow cells are visible in the primitive marrow cavity (MC). (c) The marrow cavity has gotten larger, the bony collar has gotten more complex and the chondrocytes at the periphery have enlarged. That is, they've reached the stage the interior chondrocytes were at in micrograph (a). (d) In this micrograph, very little cartilage (HC) remains in the bone's center, having been replaced with spongy bone. The surface bone on the left has begun remodeling into compact bone (note the circular regions that will become Haversian systems—see arrows). (e) The marrow cavity has been formed in this specimen through osteoclast activity on the spongy bone recently produced.

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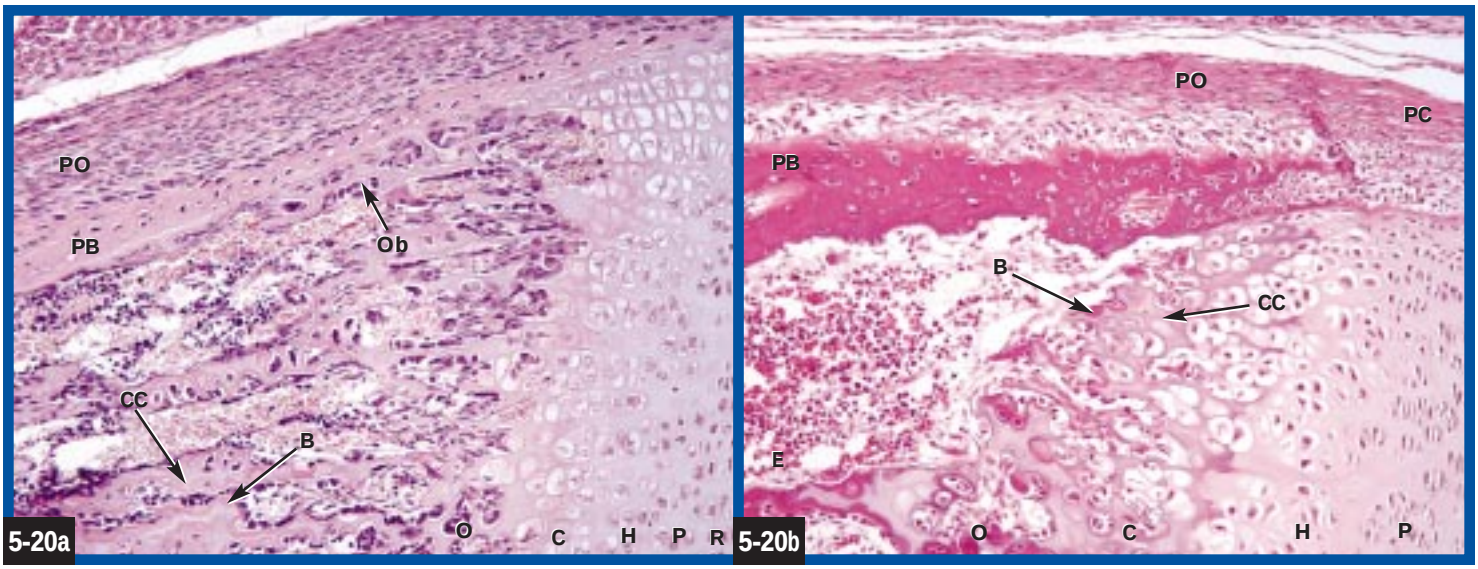
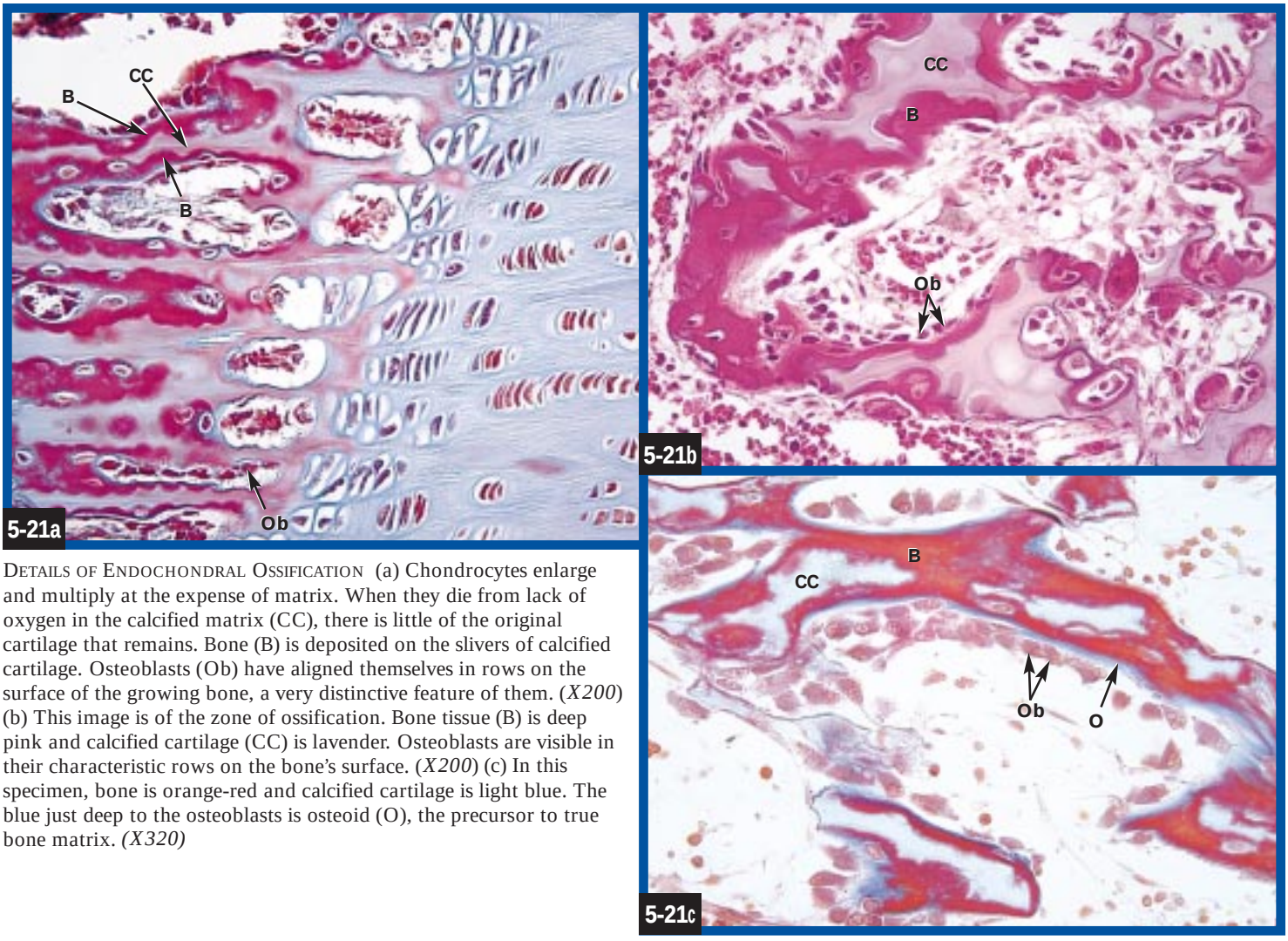


ENDOCHONDRAL OSSIFICATION IN LONGITUDINAL SECTION The zones of endochondral ossification are visible in both specimens, which are oriented so that the process is further along toward the left. Zones of reserve cartilage (R), proliferation (P), hypertrophy (H), calcification (C), ossification (O), and erosion (E) are visible, as are the periosteum (PO), perichondrium (PC), and periosteal bone (PB). (a) Bone tissue is pink in this specimen (see periosteal bone for the shade) as is calcified cartilage (which is somewhat paler). Notice how the spaces produced by deteriorated chondrocytes allow entry of osteoblasts (Ob) that deposit new bone (B) on the remaining slivers of calcified cartilage (CC). (*X100*) (b) The calcified cartilage (CC) is noticeably darker than the normal matrix in this specimen. Bone (B) is a deep pink. *(X100)*



DETAILS OF ENDOCHONDRAL OSSIFICATION (a) Chondrocytes enlarge and multiply at the expense of matrix. When they die from lack of oxygen in the calcified matrix (CC), there is little of the original cartilage that remains. Bone (B) is deposited on the slivers of calcified cartilage. Osteoblasts (Ob) have aligned themselves in rows on the surface of the growing bone, a very distinctive feature of them. (*X200*) (b) This image is of the zone of ossification. Bone tissue (B) is deep pink and calcified cartilage (CC) is lavender. Osteoblasts are visible in their characteristic rows on the bone's surface. (*X200*) (c) In this specimen, bone is orange-red and calcified cartilage is light blue. The blue just deep to the osteoblasts is osteoid (O), the precursor to true bone matrix. *(X320)*

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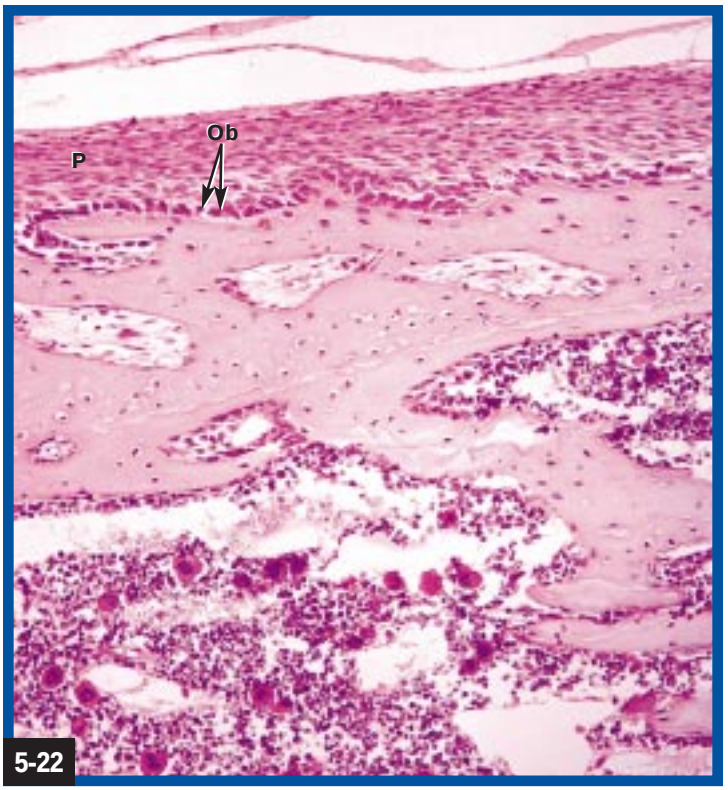
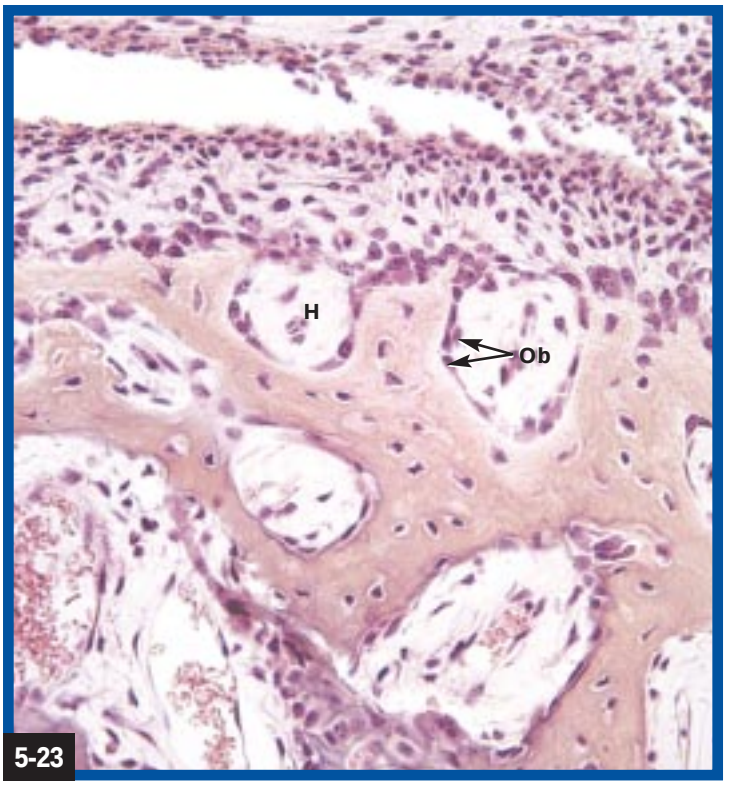
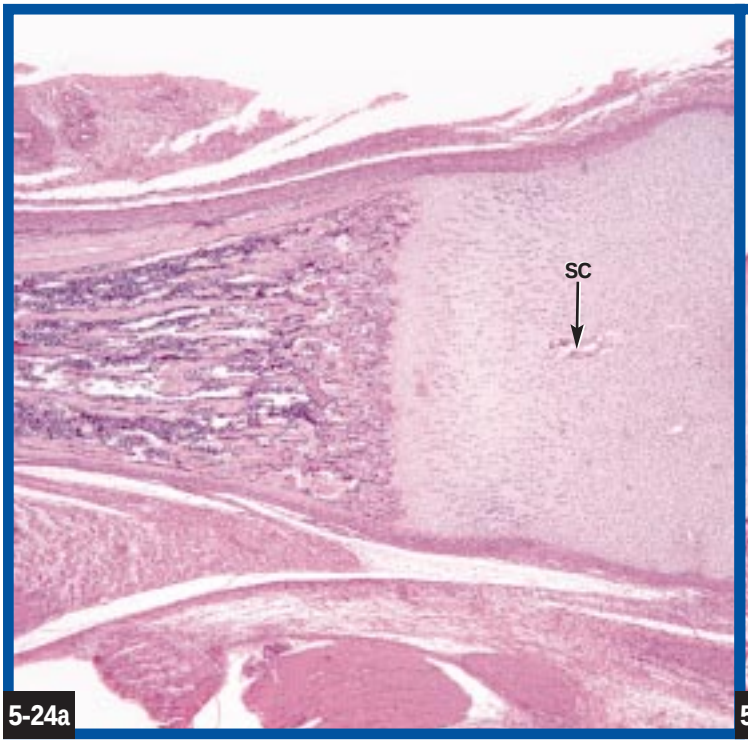
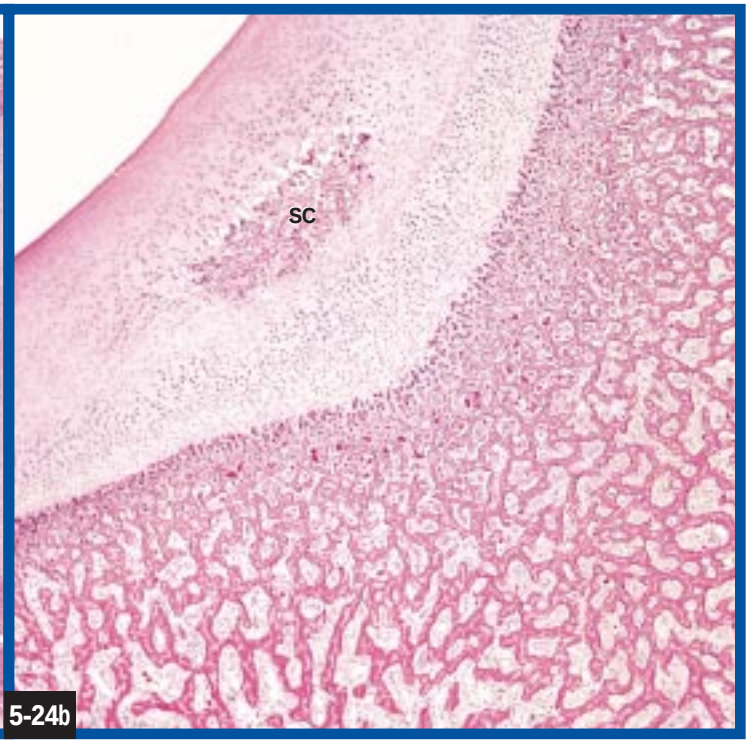


PERIOSTEAL BONE While cartilage is being replaced by bone in the interior, osteoblasts (Ob) deep to the periosteum (P) deposit bone on the outer surface of the bone at the same rate that osteoclasts remove bone from the marrow cavity. These coordinated activities result in circumferential growth of the bone. *(X130)*



SURFACE REMODELING Bone tissue is produced as spongy bone. The compact bone on bone surfaces is the result of remodeling spongy bone. Developing Haversian systems (H) are visible in this specimen. Osteoblasts (Ob) deposit concentric lamellae in the open region until all that remains is the Haversian canal with its neurovascular bundle. (*X250*)





SECONDARY CENTER OF OSSIFICATION In long bones and some other bones, a secondary center (SC) of ossification opens in the epiphysis some time after birth. The secondary center completely ossifies the epiphysis except for two regions that remain hyaline cartilage: the epiphyseal plate that connects the epiphysis and diaphysis, and the articular cartilage. Both micrographs are X25 and show early activity in the secondary center.

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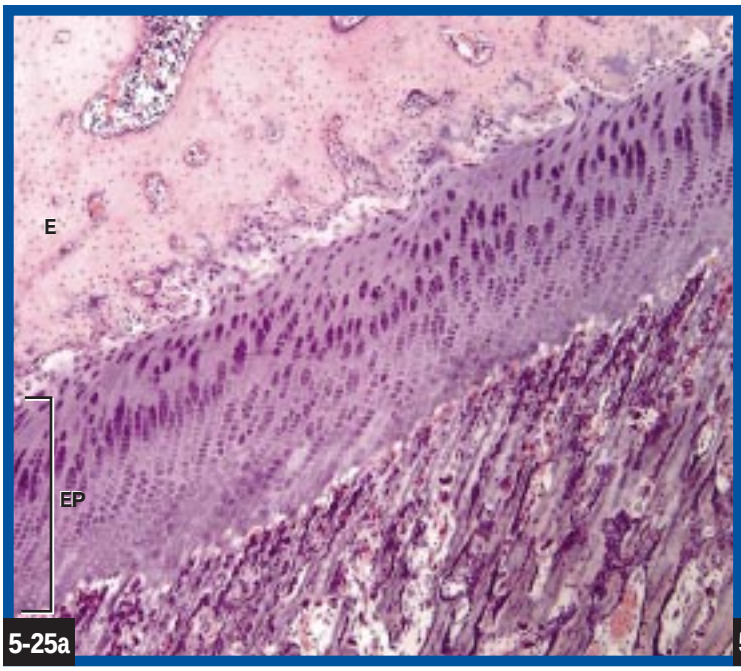
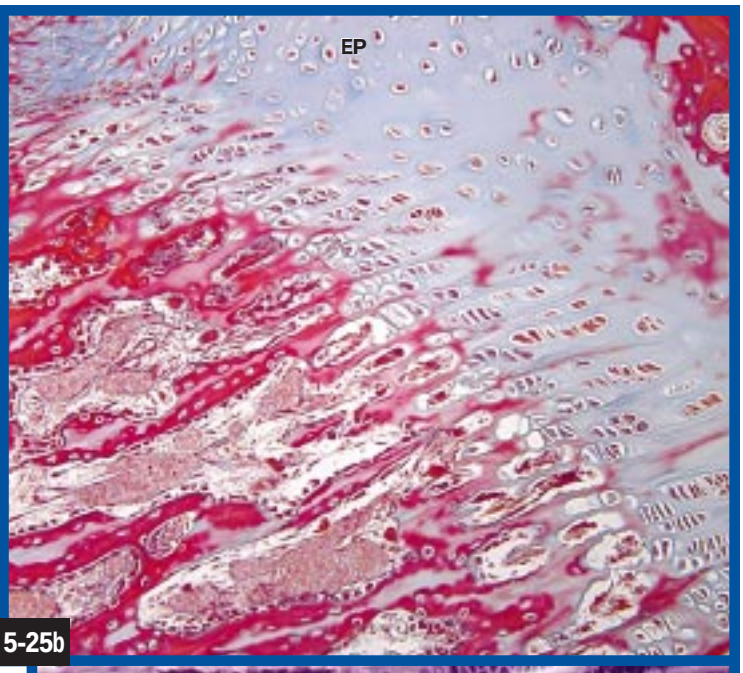
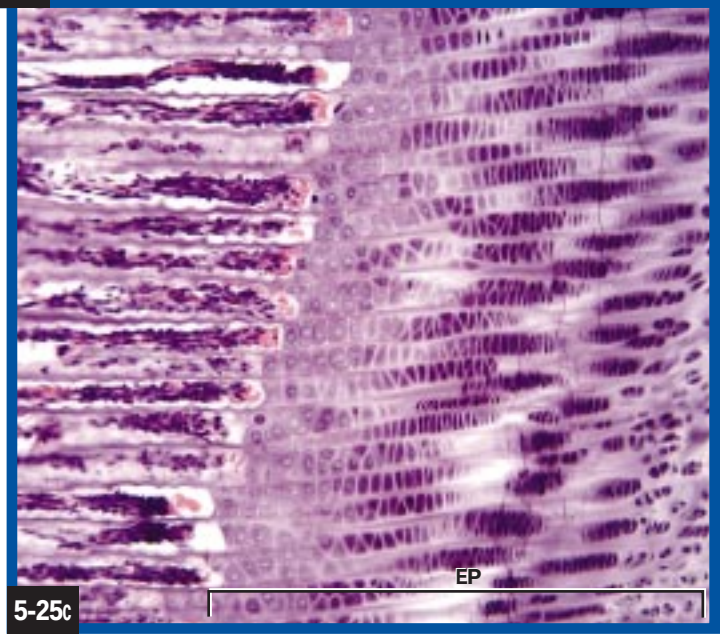
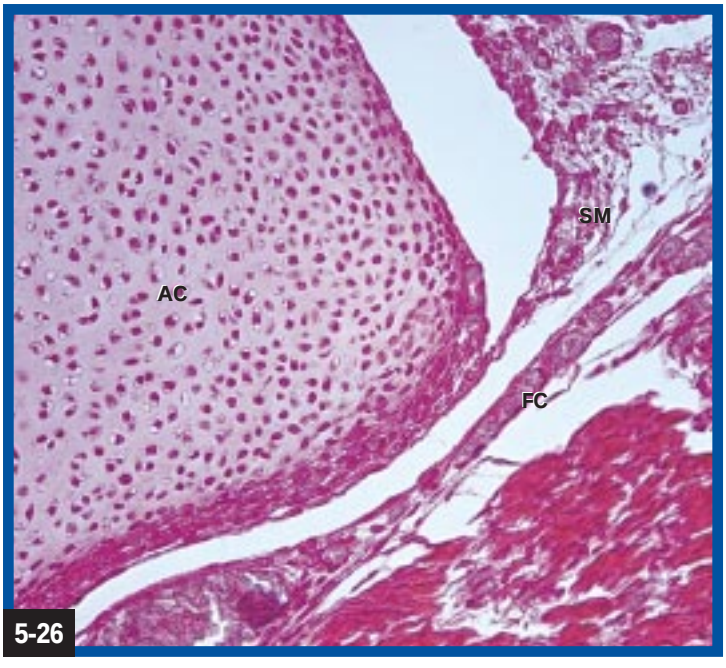






EPIPHYSEAL PLATE After birth, longitudinal growth in long bones is due to the activity of the epiphyseal plate (EP) of hyaline cartilage that joins the epiphysis with the diaphysis. All the zones of cartilage being replaced by bone are compressed into the epiphyseal plate; all are there, but there may be some overlap. New cartilage is formed on the epiphyseal side at the same rate as cartilage is replaced by bone on the diaphyseal side of the plate. (a) New bone is forming on the lower side of this epiphyseal plate, so the epiphysis (E) is being pushed upward in this micrograph. (*X50*) (b) The epiphysis is toward the upper right in this micrograph. Bone is red, reserve cartilage is light blue, and calcified cartilage is lavender. (*X100*) (c) The epiphysis is toward the right in this specimen. The stain used does not allow easy differentiation of reserve cartilage, calcified cartilage, and bone. *(X100)*



SYNOVIAL JOINT Synovial joints are freely movable. The bones involved are held together with a fibrous articular capsule (FC). The joint cavity is lined with a vascular synovial membrane (SM) that secretes a lubricating synovial fluid. Also notice the articular cartilage (AC) lacking a perichondrium. *(X100)*

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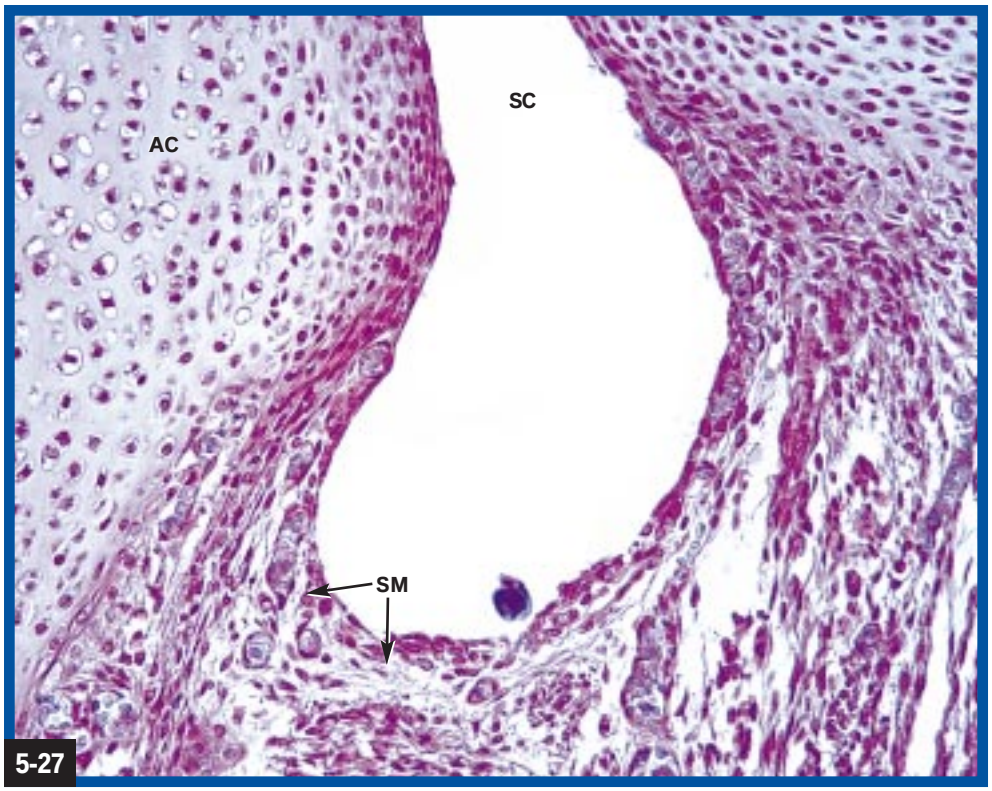
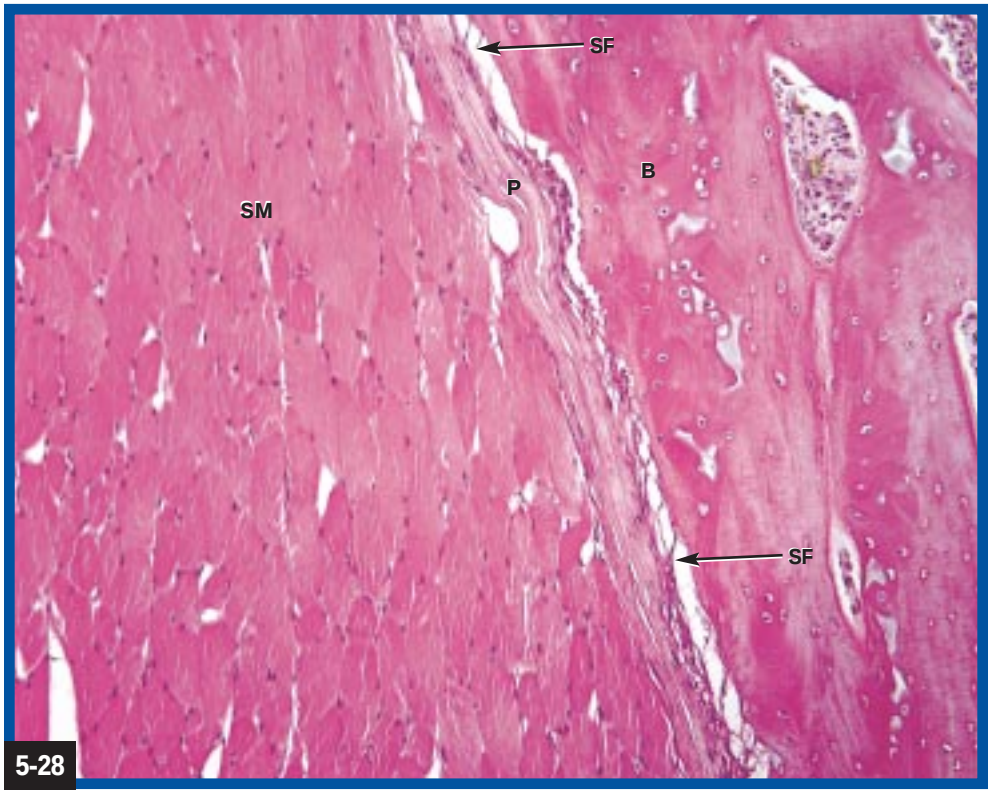


SYNOVIAL MEMBRANE The source of synovial fluid is the vascular and fibrous synovial membrane (SM). Articular cartilages (AC) of the two bones and the synovial cavity (SC) are also visible. *(X250)*



MUSCULAR ATTACHMENT TO BONE In this specimen, the connective tissue of the skeletal muscle (SM) blends with the periosteum (P), which is in turn attached to the bone (B) with Sharpey's fibers (SF). Notice that in this specimen, all tissues are pink, so identification relies on differing textures and distribution of nuclei. *(X125)*

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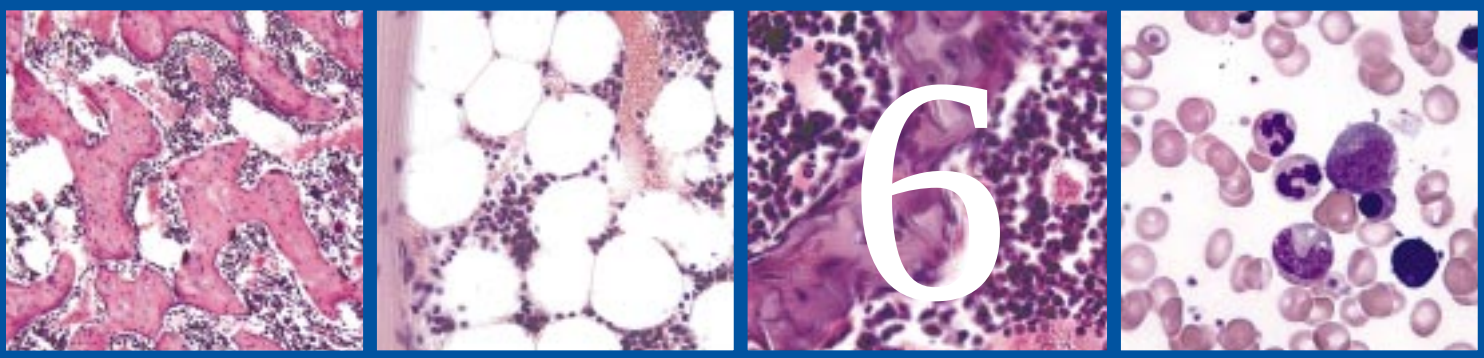
Blood and Bone Marrow

CHAPTER 6



Introduction to Blood

Blood functions as a transport medium between organs specialized for contacting and exchanging materials with the environment and the remainder of cells buried in the body. It transports oxygen from the lungs to other body cells and carbon dioxide from these same cells back to the lungs. It distributes nutrients absorbed by the small intestines and stored in the liver throughout the body, and it picks up wastes and transports them to the kidneys for excretion. In addition, it is involved in transporting cells of the body's defenses to sites where they are needed and distributing heat and hormones throughout the body.

Blood is a specialized connective tissue, with cells dispersed in a fluid intercellular material called **plasma**. Since some blood cells are not actually cells when functional, the "cellular" portion is said to be made of **formed elements.**

Formed Elements of Blood

When blood is spun in a centrifuge tube, the plasma separates from it and is found on top of the formed elements (Figure 6-1). Comprising the majority of the formed elements is a red layer made up of **erythrocytes (red blood cells, RBCs)**. On top of the erythrocytes is the narrow **buffy coat layer** made of **leukocytes (white blood cells, WBCs)** and **platelets (thrombocytes)**. The formed elements constitute 45% of the blood volume, with plasma making up the other 55%. The erythrocyte and buffy coat layers account for 44% and 1%, respectively. The following are typical cell densities for each (Figure 6-2):

- Red blood cells: 4,500,000 and 5,000,000 RBCs per cubic millimeter of blood in females and males, respectively
- White blood cells: between 6,000 and 10,000 (average 8,000) per cubic millimeter of blood
- Platelets: between 150,000 and 300,000—it is difficult to get an accurate count—per cubic millimeter of blood.

Erythrocytes (Figure 6-3) are biconcave discs with a diameter of about 7 to 8 µm. They develop from cells in bone marrow, lose most organelles (including their nucleus) during maturation, and are little more than bags of the red oxygen-carrying pigment **hemoglobin** (plus a few soluble enzymes) when functional in the blood. Their shape increases surface area for oxygen exchange and makes them pliable enough to fit through the smallest blood vessels (3 to 4 µm in diameter).

Leukocytes differ from erythrocytes in a number of ways: they are larger, nucleated, and while found in the blood during transport, usually function outside the blood. They are divided into two major groups: **granulocytes** and **agranulocytes**. Granulocytes have prominent cytoplasmic granules whose staining properties form the basis for differentiating the three major types (**neutrophils**, **eosinophils**, and **basophils**—see page 62). In addition, they have multilobed nuclei (which leads to the other name for this group: **polymorphonuclear granulocytes**) and are formed in the bone marrow. The characteristics of each granulocyte follows.

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Neutrophils (Figure 6-4) are the most abundant WBC, accounting for between 60% and 70% of all WBCs in blood. They are slightly larger than RBCs (9 to 12 µm in diameter) and have a multilobed nucleus with the lobes often joined by thin nuclear strands. Their cytoplasmic granules are unstained or are slightly lavender in standard blood smear preparations (Wright's or Giemsa stains). Functionally, they are phagocytic cells.

Eosinophils (Figure 6-5) comprise less than 5% of all WBCs in the blood. They are somewhat larger than neutrophils (10 to 14 µm in diameter) and have a two-lobed nucleus. Their cytoplasmic granules stain red in standard blood smears. They are active in combating parasitic infections, phagocytose antigen-antibody complexes, and are present during allergic reactions, apparently to temper the response.

Basophils (Figure 6-6) are rare in the blood, comprising less than 1% of all WBCs. They are slightly larger than RBCs (8 to10 µm in diameter) and have prominent, dark-purple cytoplasmic granules that make seeing the S-shaped nucleus difficult. They are involved in the inflammatory response and like mast cells, may be involved in hypersensitivity reactions.

Agranulocytes have unlobed nuclei and lack *prominent* cytoplasmic granules. (All WBCs have lysosomes that appear as faint cytoplasmic granules.) Lymphocytes and monocytes are the two types of agranulocytes.

Lymphocytes (Figure 6-7) account for between 20 and 25% of all WBCs in blood. They are slightly larger than RBCs (8 to 10 µm in diameter) and have a round nucleus that fills most of the cell, leaving only a thin ring of cytoplasm at the cell's periphery. There are three functionally distinct, but morphologically indistinguishable, types of lymphocytes. These are **B cells**, **T cells**, and **null cells**. B cells differentiate into antibody-secreting **plasma cells** when exposed to the proper antigen (Figure 6-8). They are responsible for the *humoral immune response*. T cells do not secrete antibodies in response to antigen, but they do have antigen receptors in their membranes. Depending on the type of T cell, it may initiate a *cell mediated immune response* as a **cytotoxic T cell**, or it may regulate activity of other cells either as a **T-helper** or **T-suppressor cell**. **Null cells** are so-named because they lack the membrane markers that identify T and B cells. **Natural killer (NK) cells** are null cells that kill foreign or infected cells without antigen-antibody interaction.

Monocytes (Figure 6-9) comprise between 3% and 8% of all blood WBCs. They are about twice the size of RBCs (12 to 15 µm in diameter). The cytoplasm is bluish-gray in standard blood smears and the nucleus is often indented. Monocytes are the blood form of tissue **macrophages**. In addition to phagocytic activity, some macrophages act as **antigen-presenting cells (APCs)** that phagocytose and digest foreign material, then carry the antigen on their own surface to "show" cells of the immune system and stimulate a response.

Platelets (Figure 6-10) are cell fragments derived from **megakaryocytes** in bone marrow. They are involved in the clotting process.

Composition of Bone Marrow

Marrow is found in the marrow cavity of long bones and fills spaces between trabeculae in spongy bone of all bones (Figure 6-11). It is a highly vascular tissue that contains numerous and connected blood sinusoids, a framework of reticular fibers, and cells of various types. **Red bone marrow** is found in all fetal bones, but as the individual ages, its distribution is limited to ribs, sternum, vertebrae, and flat bones of the skull. Its primary function is hemopoiesis (formation of blood cells—see below). **Yellow bone marrow** (Figure 6-12) replaces red bone marrow during aging, although it maintains the ability to revert to red marrow if the need for more blood cells arises. It contains abundant fat cells.

Postnatal Development of Blood Cells

Hemopoiesis is the production of blood cells. According to current evidence, this process begins in the bone marrow with **pluripotent stem cells** that divide to give rise to five different types of **unipotent stem cells**, each of which is responsible for producing a particular type of blood cell.

Granulopoiesis, illustrated in Figure 6-13, is the production of granulocytes. The unipotent stem cell in this series is actually bipotent, since it also can progress through the monocyte series. Each granulocyte type goes through similar developmental stages, and all begin with undifferentiated **myeloblasts** followed by **promyelocytes**, which contains primary (nonspecific) cytoplasmic granules. When a promyelocyte develops specific granules characteristic of each granulocyte it becomes a **myelocyte**. **Metamyelocytes** are smaller and have an indented nucleus. **Stab (band) cells** follow and are the last stage prior to a mature granulocyte. Stab cells are characterized by a U-shaped to slightly segmented nucleus. (By convention, if the nuclear indentation is less than half the nuclear diameter, the cell is a metamyelocyte. If more than half of the nuclear diameter, it is a stab cell.) Mature granulocytes have the segmented or lobed nucleus and appear as they do in blood. Examples of developmental stages are shown in Figure 6-14.

Monopoiesis is the production of monocytes (Figure 6-15). Monocytes develop from the same stem cell as granulocytes and pass through **monoblast** and **promonocyte** (Figure 6-16) stages before the mature monocyte is formed. During development, the cells become smaller and the nuclear indentation becomes more prominent. Both of these are rare in bone marrow smears.

Lymphopoiesis is the production of lymphocytes (Figure 6-17). **Lymphoblasts** and **prolymphocytes** are the developmental stages a lymphocyte passes through prior to maturity. These are differentiated primarily by size, with the cells

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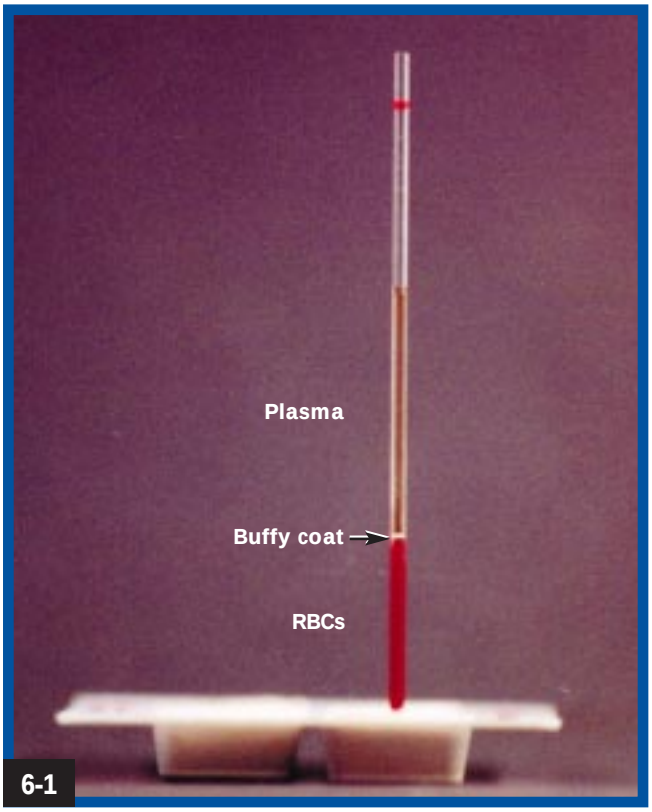
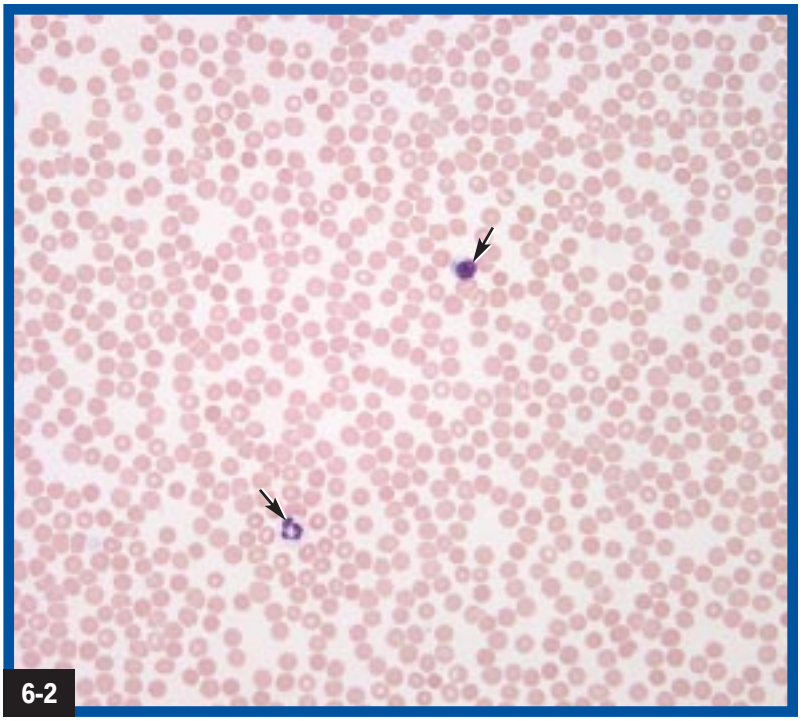
becoming smaller with maturity, but they are rarely seen in normal bone marrow. A mature lymphocyte is shown in Figure 6-16.

Erythropoiesis is the process of RBC formation and the sequence is shown in Figure 6-18. Examples of these cells are shown in Figure 6-19. It begins with the **proerythroblast**, a large cell with a prominent nucleus, little basophilic cytoplasm, and no hemoglobin. The proerythroblast develops into a series of **erythroblasts (normoblasts)** that show a progressive decrease in size, a loss of organelles (along with a loss of basophilic staining), and an increase in hemoglobin (along with increasing eosinophilia). The stages are **basophilic erythroblast**, **polychromatophilic erythroblast**, and **orthochromatophilic erythroblast**. The orthochromatophilic erythroblast has a pinkish cytoplasm and a small, densely staining nucleus. The final developmental stage before the cell is a mature RBC is the **reticulocyte**. It is anucleate and appears very similar to RBCs except its cytoplasm contains a bluish network when stained with brilliant cresyl blue.

Thrombopoiesis (Figure 6-20) is the production of platelets. **Megakaryocytes** are derived from a unipotent stem cell, which undergoes several mitotic divisions as a **megakaryoblast** without cytokinesis. The resulting megakaryocyte is a large (up to 100 µm in diameter), polyploid cell with a lobed nucleus. It produces platelets by cytoplasmic fragmentation. These cells are shown in Figures 6-21 and 6-22.



HEMATOCRIT This capillary tube contains blood that has been centrifuged to separate the plasma (above) from the formed elements (below). A thin buffy coat (composed of white blood cells and platelets) is visible at the RBC and plasma junction.



BLOOD SMEAR Blood is usually examined as a smear on a slide stained with either Giemsa (as in this preparation) or Wright's stain. RBCs outnumber WBCs about 1000 to 1. Two WBCs are visible in this field (arrows). *(X265)*

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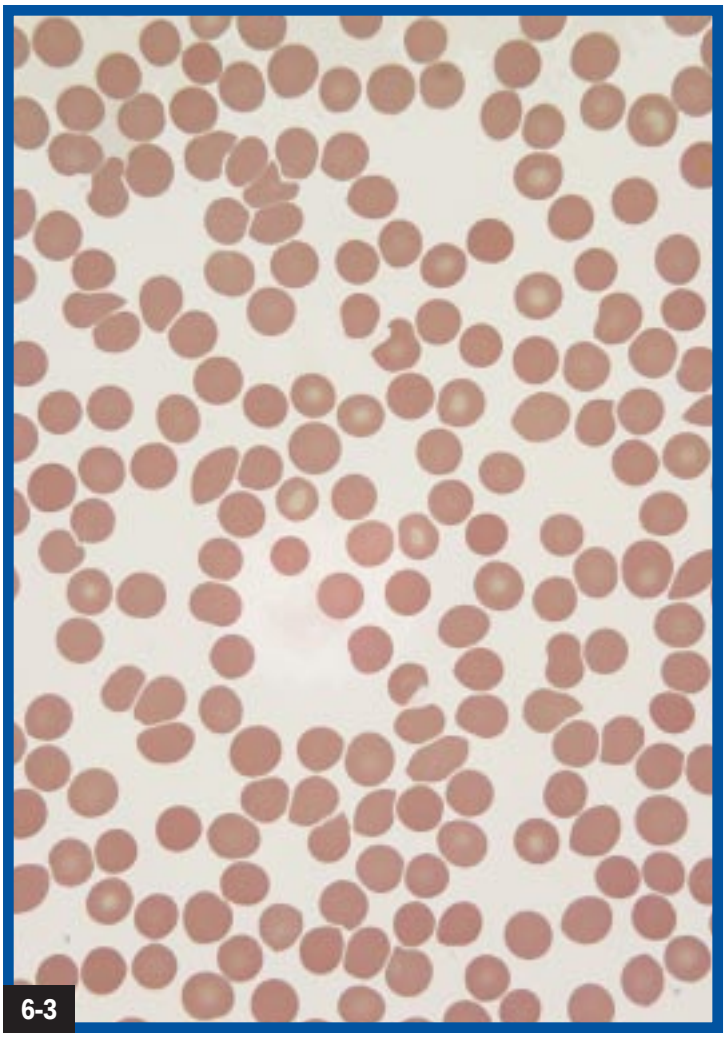
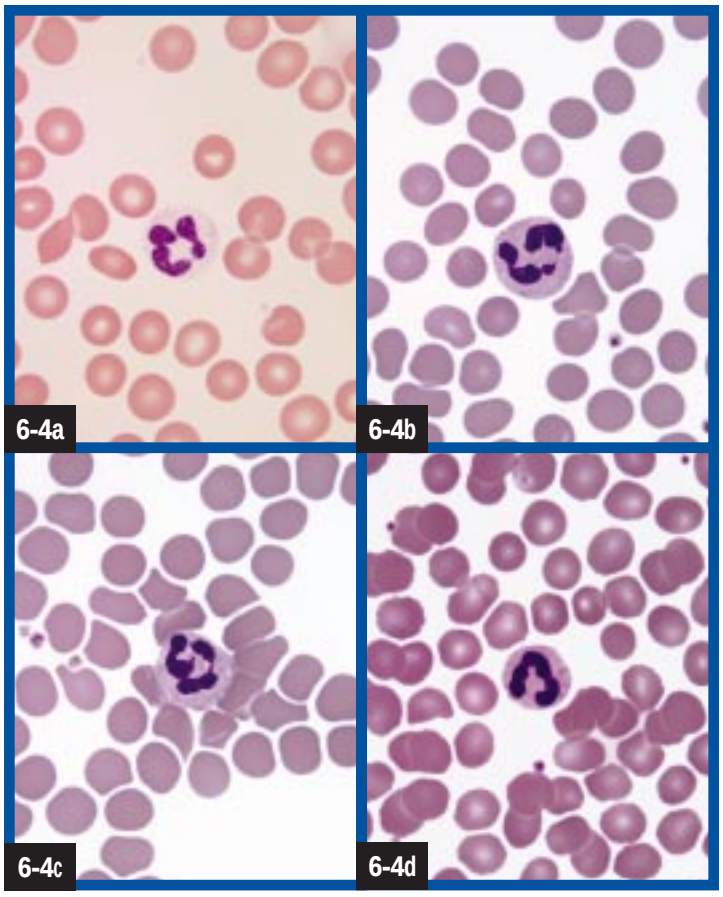
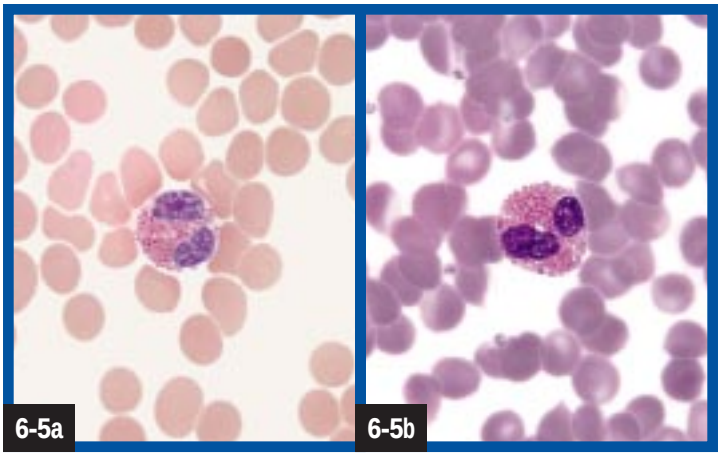


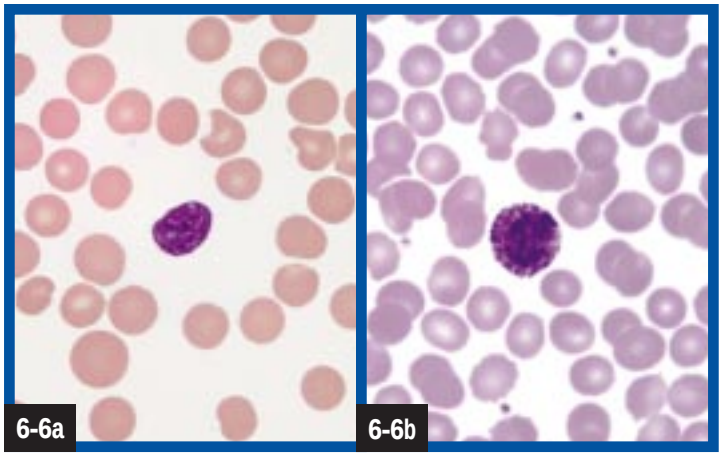
RED BLOOD CELLS The biconcave disk shape of the RBCs is visible in some cells in this Giemsa preparation. RBCs are very sensitive to osmotic conditions and their shape may change if the staining conditions are not isosmotic. *(X660)*



NEUTROPHILS Neutrophils are granulocytes with a pinkish to gray cytoplasm. They are the most abundant WBC and are slightly larger than RBCs. Mature neutrophils have a segmented nucleus (as in micrographs a, b, and c). Immature neutrophils have an unsegmented nucleus and are called band cells (as in micrograph d). About 30% of neutrophils in blood samples from females demonstrate a "drumstick" protruding from the nucleus, as in (c). This is the region of the inactive X chromosome. Micrograph (a) was stained with Giemsa stain; the others were prepared with Wright's stain. All photos are X660.



EOSINOPHILS These granulocytes are relatively rare and are about twice the size of RBCs. Their cytoplasmic granules stain red, and their nucleus usually has two lobes. Micrograph (a) was prepared with Giemsa stain; (b) was prepared with Wright's stain. Both were magnified X660.



BASOPHILS Basophils comprise only about 1% of all WBCs. They are slightly larger than RBCs and have dark purple cytoplasmic granules that obscure the nucleus. Both micrographs are X660. Micrograph (a) was prepared with Giemsa stain and (b) was prepared with Wright's stain.

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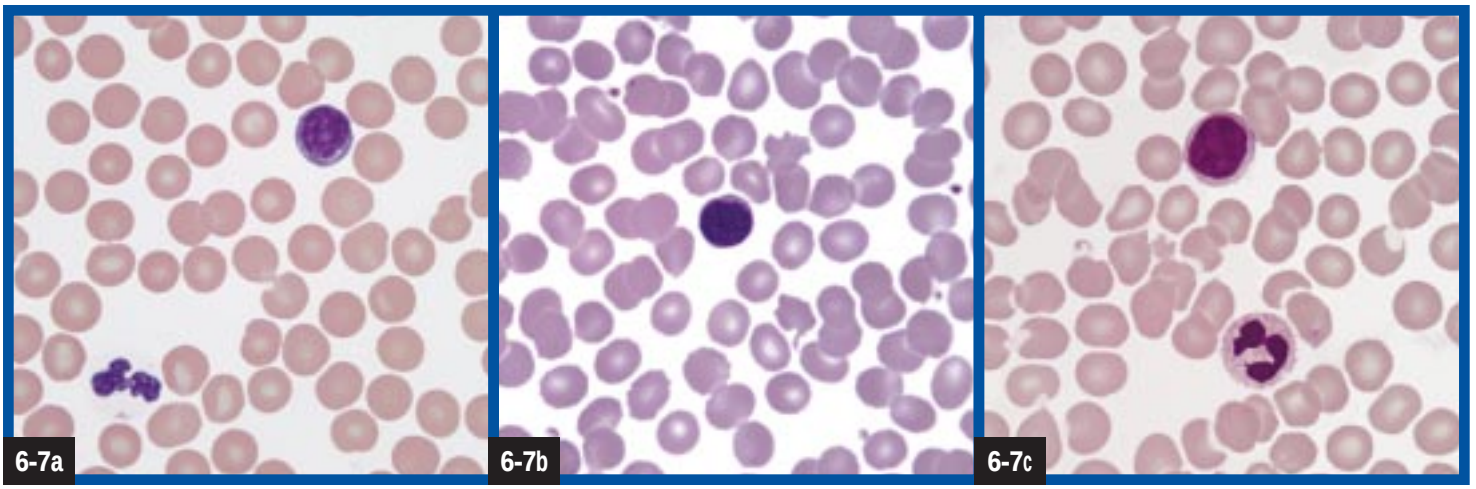
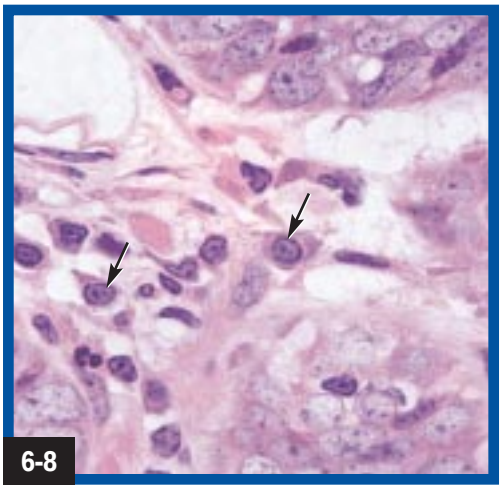
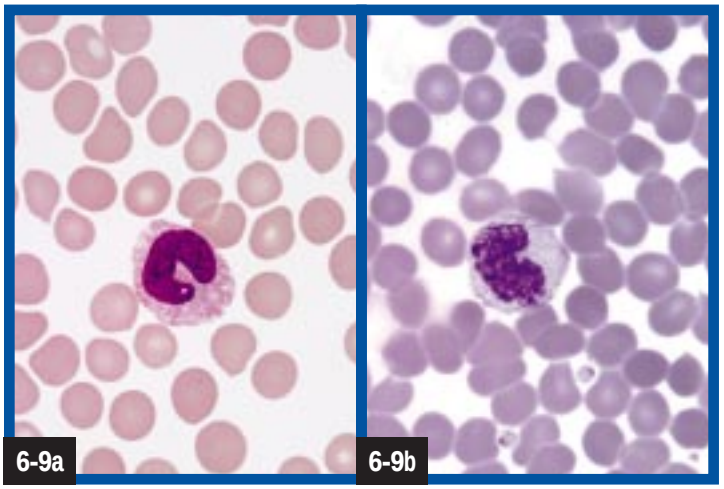


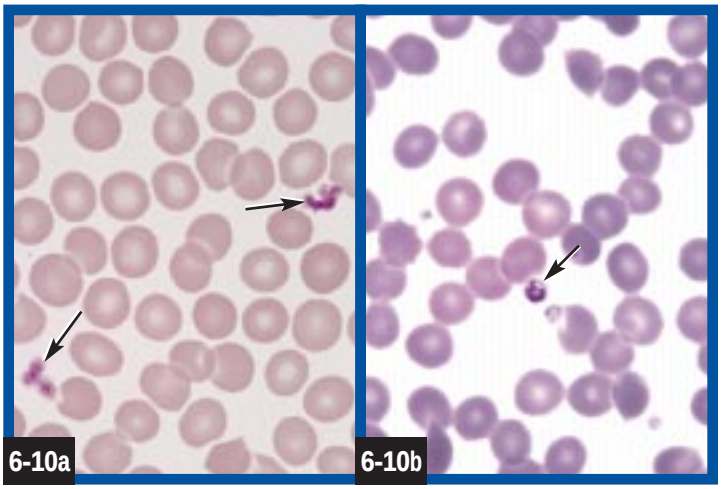
LYMPHOCYTES Lymphocytes are common in the blood, comprising up to 25% of all WBCs. Most are about the size of RBCs and have only a thin halo of cytoplasm encircling their round nucleus. They belong to functional groups called B cells and T cells, which are morphologically indistinguishable. Micrographs (a) and (b) are small lymphocytes and were prepared with Giemsa and Wright's stains respectively. Some lymphocytes are larger, as in micrograph (c). These are natural killer (NK) cells or some other type of "null" cell. A neutrophil is also seen in (c). All micrographs are X660.



PLASMA CELLS B lymphocytes develop into plasma cells when stimulated by the appropriate antigen. Plasma cells secrete protective antibodies against the antigen. These plasma cells (arrows) are recognizable because of their elongated shape, eccentric nucleus with "clock face" chromatin, and a pale region near the nucleus (which is the site of a Golgi apparatus). This specimen is from the colon. *(X660)*



MONOCYTES Monocytes are the blood form of macrophages. They are about twice the size of RBCs and have a round or indented nucleus. Both micrographs are X660. (a) Giemsa stain. (b) Wright's stain.



PLATELETS Platelets (arrows) are cell fragments involved in clotting. (a) Giemsa stain. (b) Wright's stain. Both micrographs are X660.

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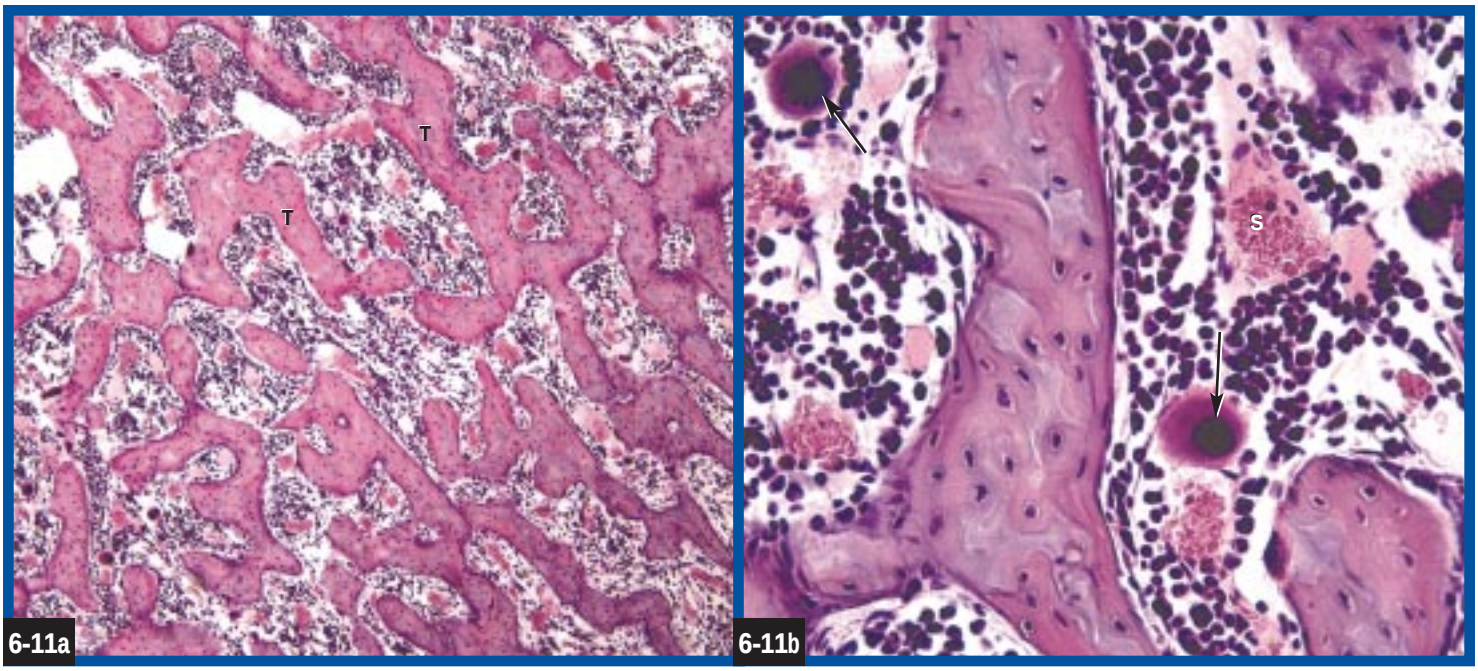
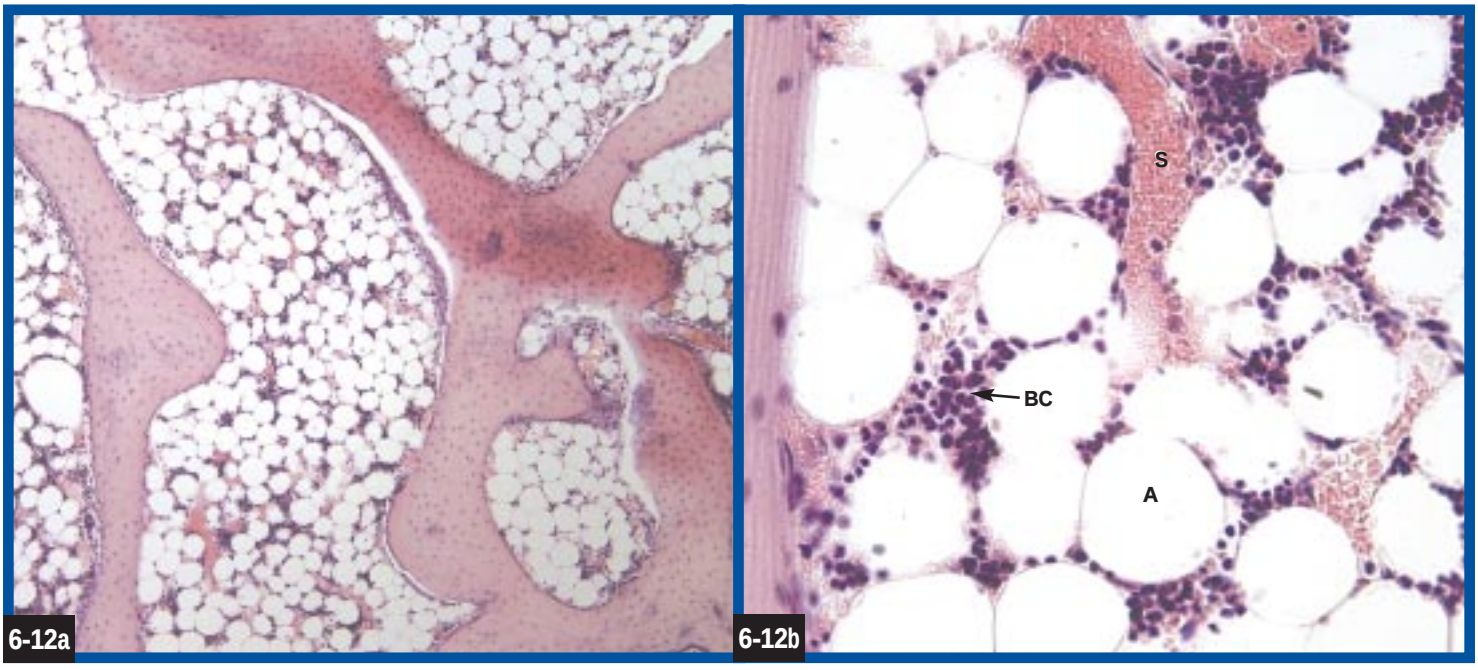


RED MARROW The spaces between trabeculae of spongy bone (T) are often filled with red marrow. It consists of various developmental stages of blood cells. (a) X50. (b) Blood sinusoids (S), marrow cells, and two megakaryocytes (arrows) are visible. *(X250)*



YELLOW MARROW In most bones, red marrow is replaced by yellow marrow in the adult. The majority of cells are adipocytes. (a) X50. (b) Adipocytes (A), sinusoids (S), and some remaining blood cells (BC) are seen. *(X250)*

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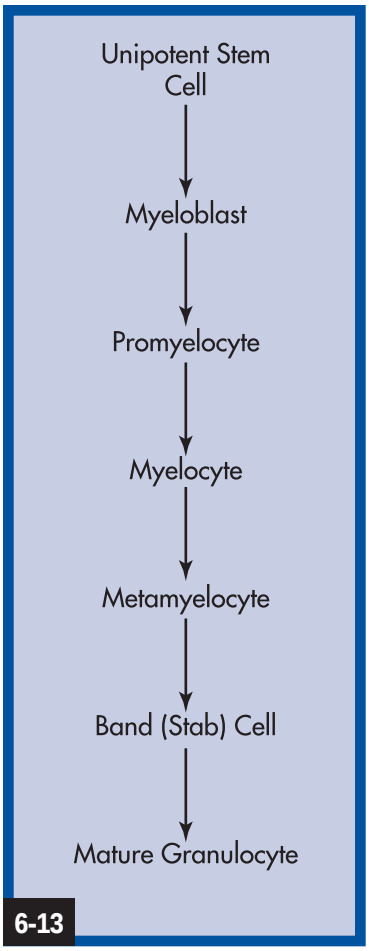
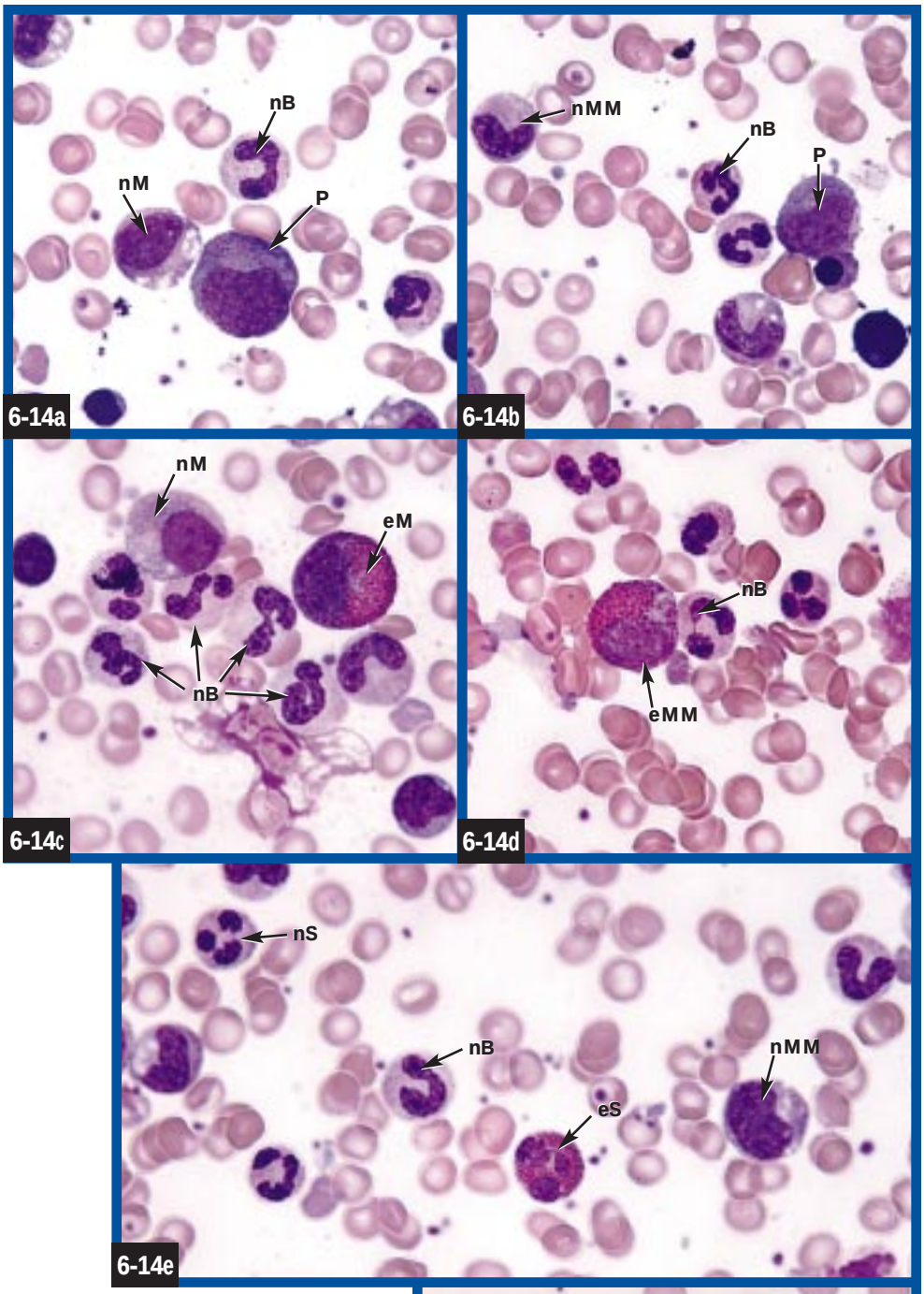
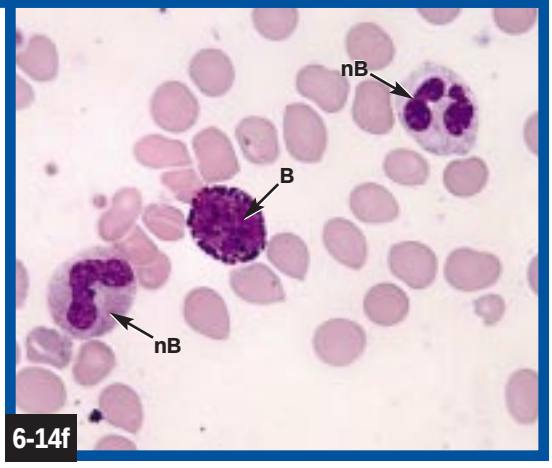


GRANULOCYTE DEVELOPMENT Through the promyelocyte stage, the precursors of neutrophils, basophils, and eosinophils are indistinguishable. Once myelocytes begin accumulating granules specific to each granulocyte, each developmental series can be traced separately. The overall pattern involves accumulation of cytoplasmic granules and progressive indentation and segmentation of the nucleus.





BONE MARROW SMEARS ILLUSTRATING GRANULOCYTE DEVELOPMENT These marrow smears illustrate most of the cells in the granulocytic developmental series. Some cells will be encountered frequently (*e.g.*, neutrophilic cells) whereas others are much less common (*e.g.*, basophils). (a through f X660) Key to the symbols used: **MB** = myeloblast, **P** = promyelocyte, **nB** = neutrophilic band, **nM** = neutrophilic myelocyte, **nMM** = neutrophilic metamyelocyte, **nS** = neutrophilic segmented, **eM** = eosinophilic myelocyte, **eMM** = eosinophilic metamyelocyte, **eS** = eosinophilic segmented, **B** = basophilic myelocyte.

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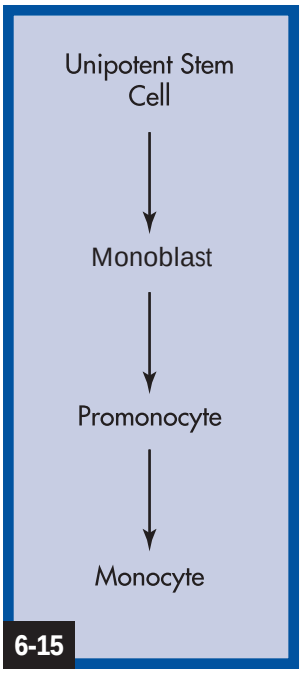
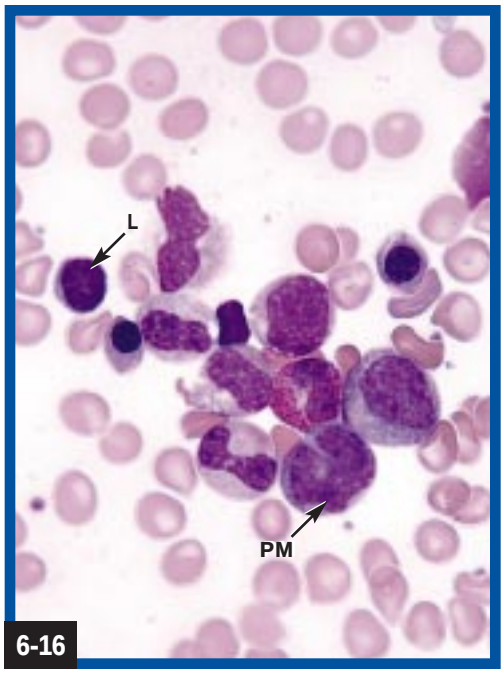
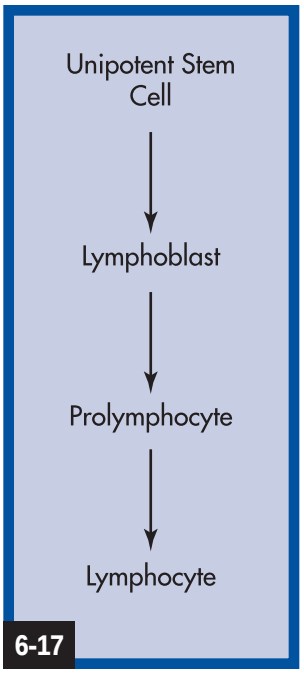


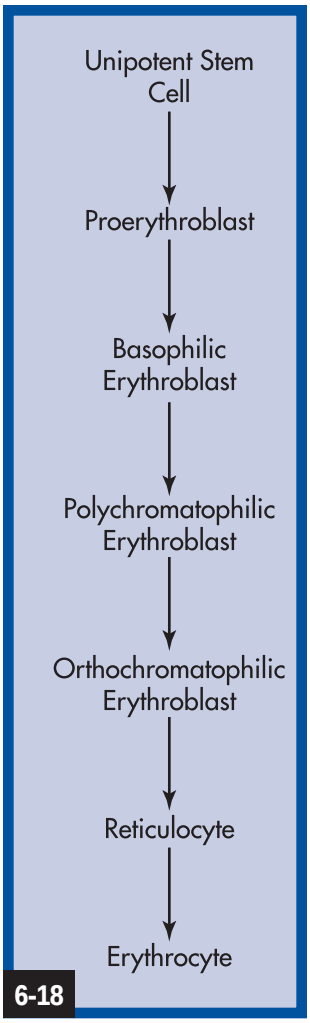
MONOCYTE DEVELOPMENT The unipotent stem cell is the same cell that gives rise to the granulocytic cells. Cells of monocyte development are difficult to find in marrow smears.



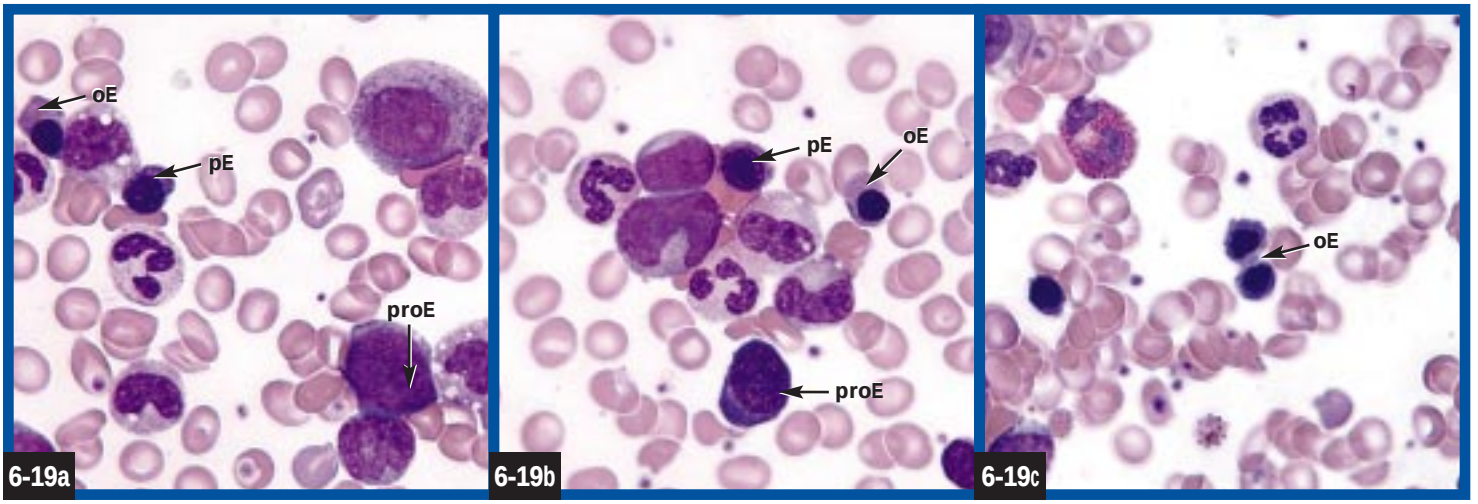
BONE MARROW SMEAR ILLUSTRATING MONOCYTE AND LYMPHOCYTE DEVELOPMENT The precursors of lymphocytes and monocytes are relatively rare in marrow smears. Shown here are a promonocyte (PM) and lymphocyte (L). Early stages of lymphocyte development are often difficult to tell apart. If there is doubt as to a cell's identity, by convention it is just called a lymphocyte. *(X660)*



LYMPHOCYTE DEVELOPMENT Lymphocytes go through only two stages in development in marrow. Unlike other blood cells, they continue their development outside the marrow in lymphoid tissue throughout the body.



ERYTHROCYTE DEVELOPMENT The major changes in erythrocyte development are a decrease in size, loss of organelles (most notably, the nucleus) and an increase in cytoplasmic hemoglobin.



BONE MARROW SMEARS ILLUSTRATING ERYTHROCYTE DEVELOPMENT (a through c X660) Key to symbols used: **proE** = proerythroblast, **pE** = polychromatophilic erythroblast, **oE** = orthochromatophilic erythroblast. Note the oE extruding its nucleus in (b) and the dividing oE in (c). Both are indicated with arrows.

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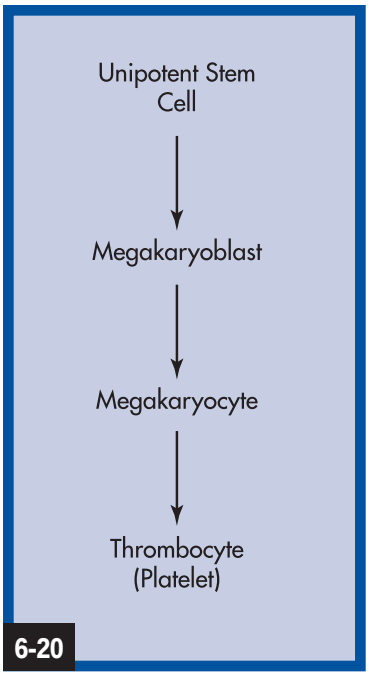
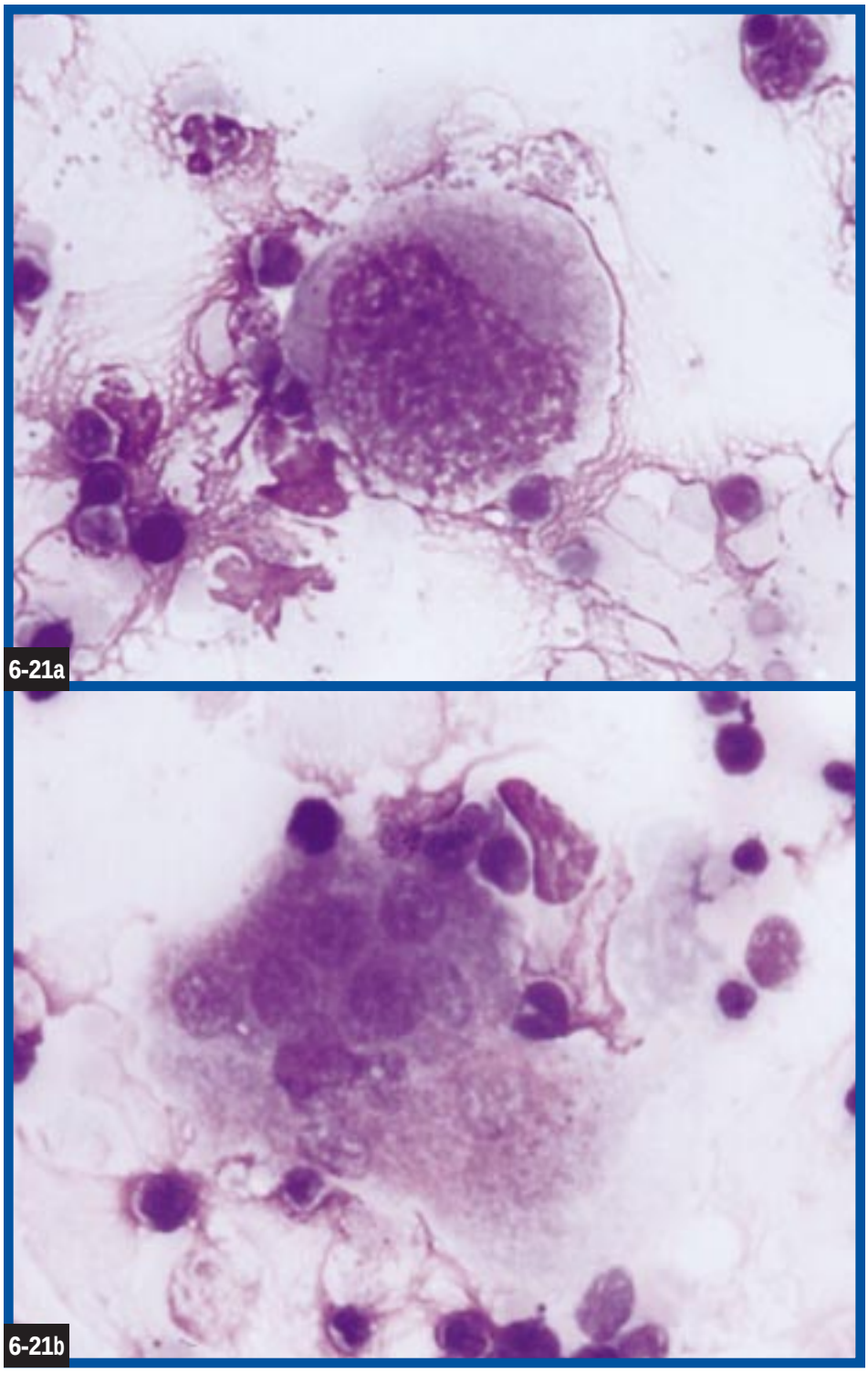


THROMBOCYTES (PLATELET) DEVELOPMENT Megakaryoblasts develop into megakaryocytes by repeated mitotic divisions without cytokinesis. Once formed, megakaryocytes undergo fragmentation to produce hundreds of thrombocytes.



BONE MARROW SMEARS ILLUSTRATING THROMBOCYTE DEVELOPMENT (a) Megakaryoblast with a single, unlobed nucleus. (*X400*) (b) The characteristic lobed nucleus in this megakaryocyte is visible. *(X400)*

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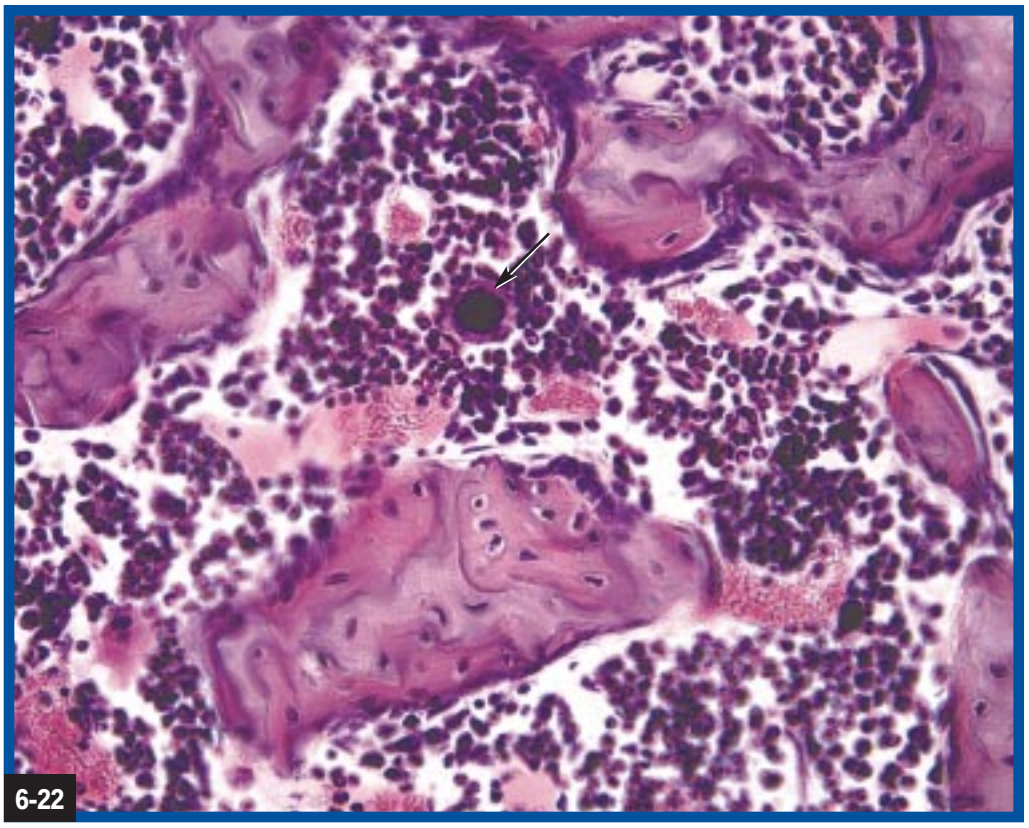

SECTION OF BONE MARROW Because of its size, this megakaryocyte (arrow) stands out against the marrow cells. *(X265)*

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Muscle Tissue

CHAPTER

Introduction to Muscle Tissue

Muscle tissue is a highly cellular and vascular tissue specialized for contraction. Contraction of muscle results in movement of a body part, propulsion of a substance, or in some instances, stopping movement of a substance.

There are three basic types of muscle tissue: **skeletal muscle**, **cardiac muscle**, and **smooth (visceral) muscle**. The cells of all muscle tissues are long and thin, and are referred to as **muscle fibers**.

Characteristics of Skeletal Muscle

Skeletal muscle (Figure 7-1) is associated with the bones of the skeleton and is responsible for movement of the body. It also may be found associated with the skin (as in the muscles of facial expression) and with some viscera (the proximal end of the esophagus, for example). In all cases, skeletal muscle is under voluntary control.

The fibers of skeletal muscle are long (up to 3 cm) with a diameter between 10 and 100 µm. They are multinucleate, with their nuclei pushed to the periphery of each fiber (Figure 7-2). With the light microscope, alternating dark and light bands are visible, giving the fibers a striped or striated appearance (Figure 7-3). The dark striations are called **A bands**, whereas the lighter ones are known as **I bands**. A thin **Z disc** bisects each I band. With electron microscopy, it is seen that the striations are the product of the highly organized arrangement of actin and myosin filaments within each fiber (Figure 7-4). It is these filaments that form the contractile apparatus and cause fiber shortening by a mechanism known as the sliding filament theory. In this model, the contractile unit is the region between two Z discs and is called a **sarcomere**. During contraction, the Z discs are brought closer together. As the actin and myosin filaments slide across one another, the I bands become narrower but the A bands stay the same width.

Skeletal muscle tissue is combined with connective tissues to form specific muscle organs, like the biceps brachii or gluteus maximus. The connective tissue components of a muscle weave between the muscle fibers and bind the whole organ together. Covering the entire muscle is **epimysium** (Figure 7-5), a dense irregular collagenous tissue layer. Smaller extensions of epimysium penetrate the muscle as **perimysium** and surround several fibers forming a **fascicle**. Extending from the perimysium is a fine layer of reticular tissue and basal lamina called **endomysium** that surrounds each individual fiber. These connective tissue layers are all continuous with the connective tissue of the muscle's tendon, which in turn attaches to the bone's periosteum (Figures 7-6 and 7-7). In addition, many of the connective tissue fibers in the tendon are attached directly to the membranes of the muscle fibers. Thus, when a muscle contracts, it pulls on its connective tissue (including its tendon) which transmits the pull to the bone and moves it.

Muscle fibers can be classified as one of three types based on diameter, amount of myoglobin (structurally similar to hemoglobin and also acts in oxygen transport), rate of contraction, and other features. The fiber types are **red slow twitch fibers**, **white fast twitch fibers**, and **intermediate fibers** (Figure 7-8). Red fibers are red because of their abundance of

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myoglobin. They have a smaller fiber diameter, have a low glycogen content, and are capable of slower and weaker contractions than white fibers, but do not fatigue as easily. White fibers have less myoglobin and more glycogen than red fibers. They also are larger, contract more rapidly and with greater strength, but fatigue easily. Intermediate fibers are intermediate between white and red fibers in these characteristics. All muscles have all fiber types, but the proportions differ depending on the primary role played by the muscle. Red fibers are abundant in postural muscles, whereas white fibers predominate in appendicular muscles.

Each skeletal muscle fiber is supplied (innervated) by a somatic motor neuron. The structure formed between the muscle fiber and its somatic motor neuron is a **motor end plate** (Figure 7-9). While not visible in light micrographs, there is an actual gap between the membranes of the neuron and muscle fiber called a synapse. When a nerve impulse reaches the end of the neuron a neurotransmitter (acetylcholine) is released into the synapse, diffuses across it, and stimulates the muscle cell to contract.

Muscle spindles (Figure 7-10) are sensory organs in skeletal muscles that detect stretching. They are formed from modified muscle fibers and somatic sensory neurons. If stretched, they initiate a stretch reflex that results in contraction.

Characteristics of Cardiac Muscle

Cardiac muscle tissue (Figure 7-11) is found only in the heart where it forms the **myocardium**, the thickest layer of the heart wall. The tissue is under involuntary control and has the innate ability to contract rhythmically, although the nervous system and hormones can modify contraction rate.

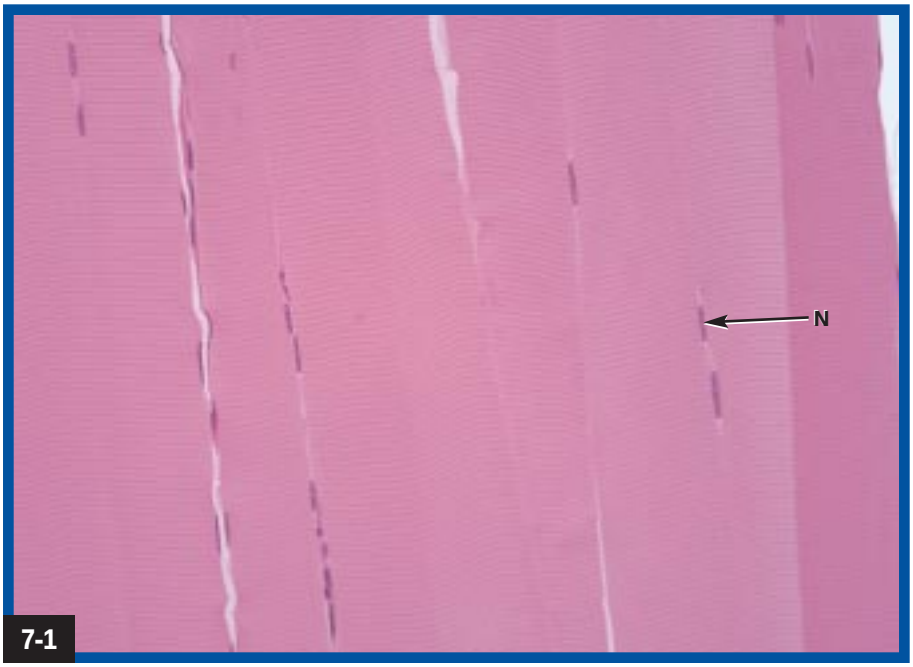
Cardiac muscle fibers are striated, branched, and uninucleate (occasionally two nuclei are present), with the oval nucleus found near the fiber's center (Figure 7-12). They are less than 100 µm long and about 15 µm in diameter. **Intercalated discs** (Figure 7-13), found at the junctions between cells, are seen as dark transverse lines with the light microscope. They physically bind the cells together so the force of contraction is transmitted between the linked cells. They also promote the rapid spread of electrical action potentials from cell to cell.

Cardiac muscle is very vascular, with abundant capillaries visible between fibers (Figure 7-14). An **endomysium** of collagenous fibers is also present.

Characteristics of Smooth Muscle

Smooth muscle (Figure 7-15) is found in the walls of organs, so it is also known as **visceral muscle**. It is under involuntary control and is capable of slow, sustained contractions. (Think of the uterus during childbirth!) Smooth muscle fibers are long and tapered at both ends with a single, central nucleus conforming to the cell's shape (Figure 7-16). There are no striations.

Two layers of smooth muscle are often in the walls of tubular organs, with the fibers of one layer running the length of the organ and the fibers of the other layer oriented around the organ (Figure 7-17). These **longitudinal** and **circular layers** are capable of producing a specialized form of contraction in tubular organs called peristalsis.



SKELETAL MUSCLE Transverse Striations and many peripheral nuclei (N) characterize skeletal muscle fibers. *(X230)*

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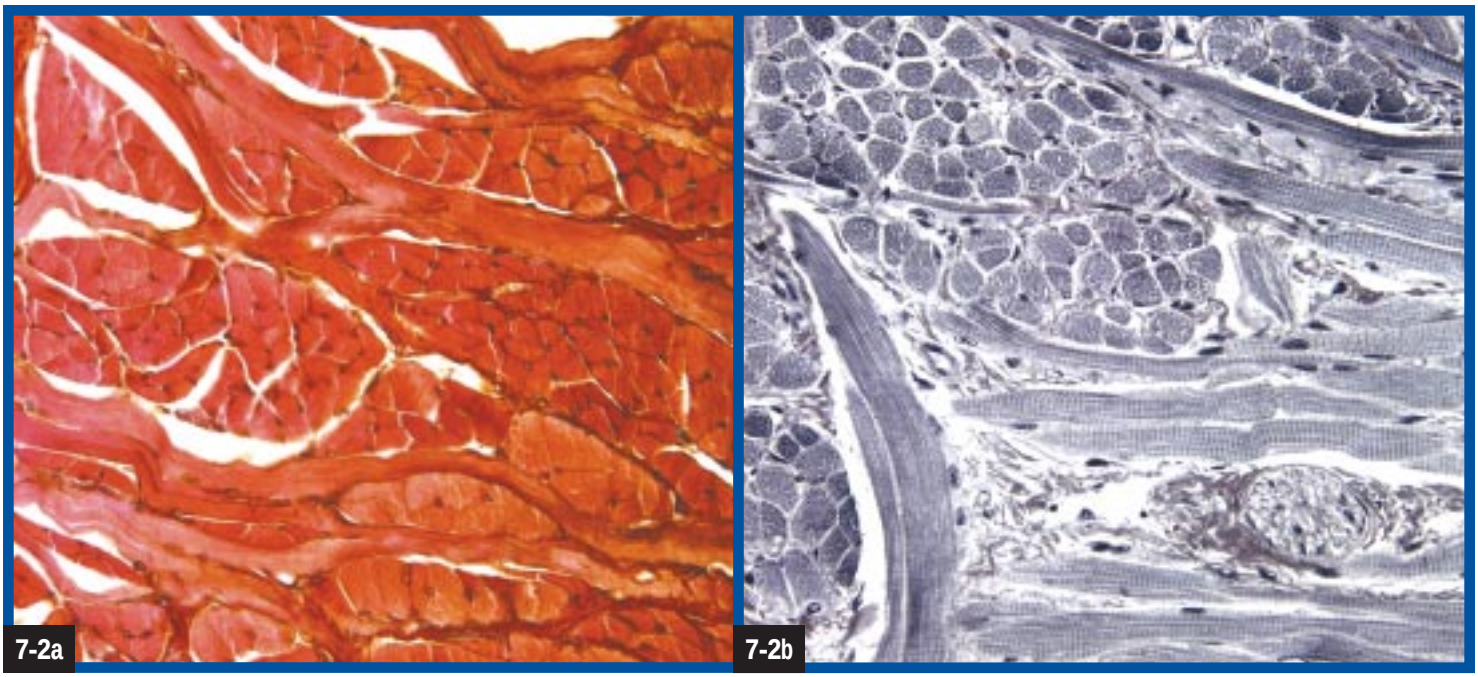
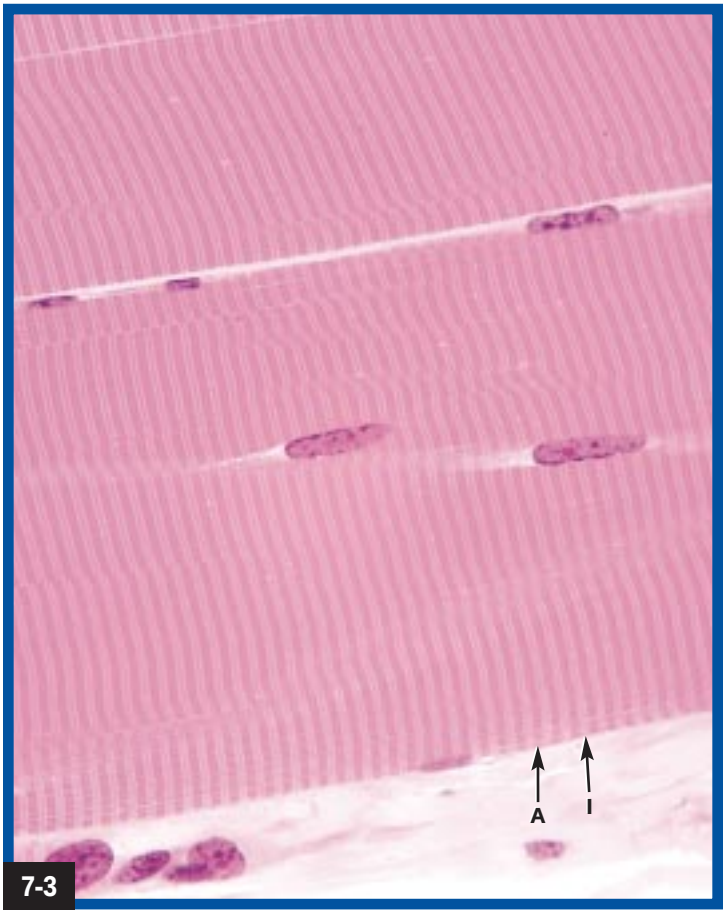


SKELETAL MUSCLE IN VARIOUS SECTIONS These specimens from the tongue show skeletal muscle fibers sectioned in all planes. Even though the striations are not visible in cross section, the peripheral nuclei are a useful feature for identifying this tissue. Both micrographs are X210.



STRIATIONS In the light microscope striations are seen as thick dark stripes (A bands) and faintly visible thin dark lines (Z discs) bisecting thick light stripes (I bands). Notice that the nuclei are not in the striated part of the cell. *(X630)*

THE SARCOMERE The orderly arrangement of actin and myosin filaments accounts for the striations in skeletal muscle. In addition to the Z discs and A and H bands, an M disc within the H band is visible. The contractile unit of skeletal muscle is the sarcomere, the region between Z discs. During contraction, the interdigitating filaments slide across one another and the Z discs are brought closer together. As a result, I bands disappear. The I bands in this specimen are narrow because the muscle is in a contacted state. *(X22,000)*

(Courtesy of UCSD Medical Center)

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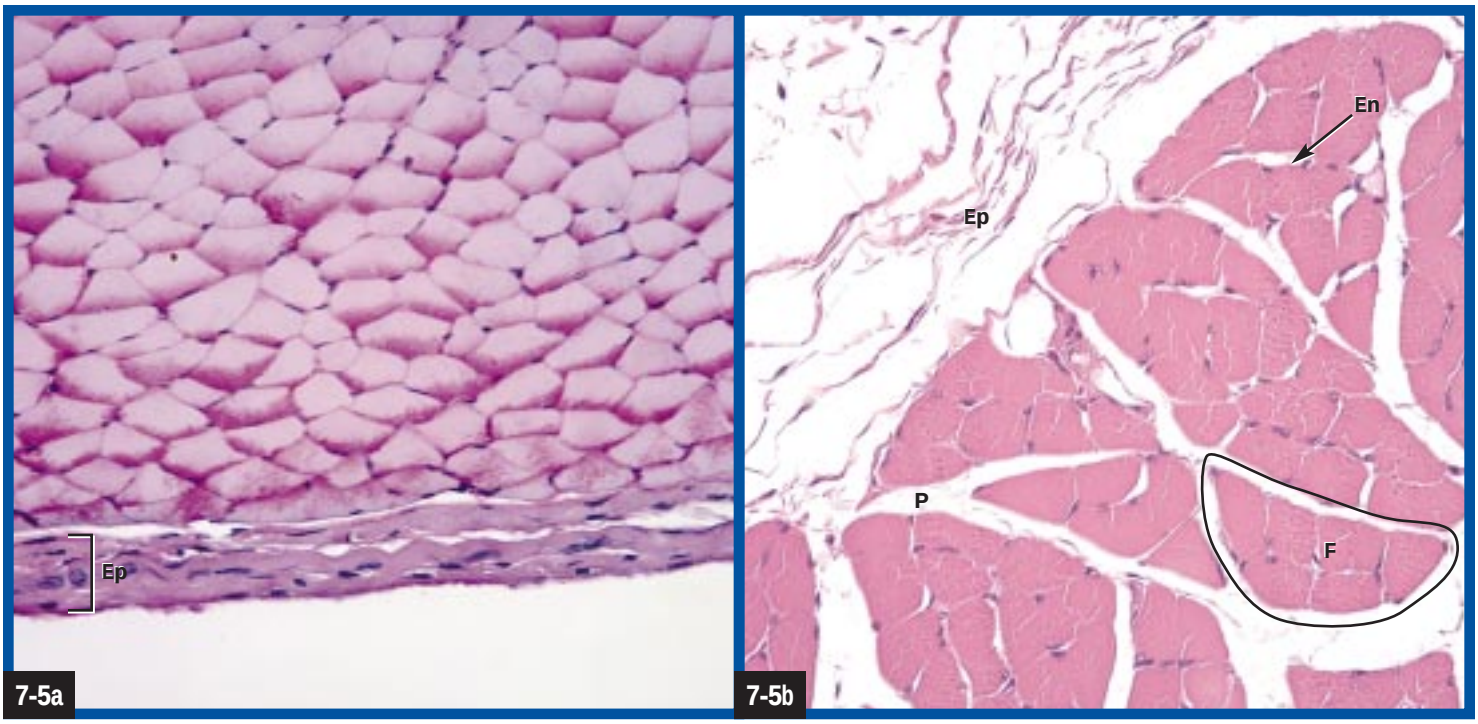
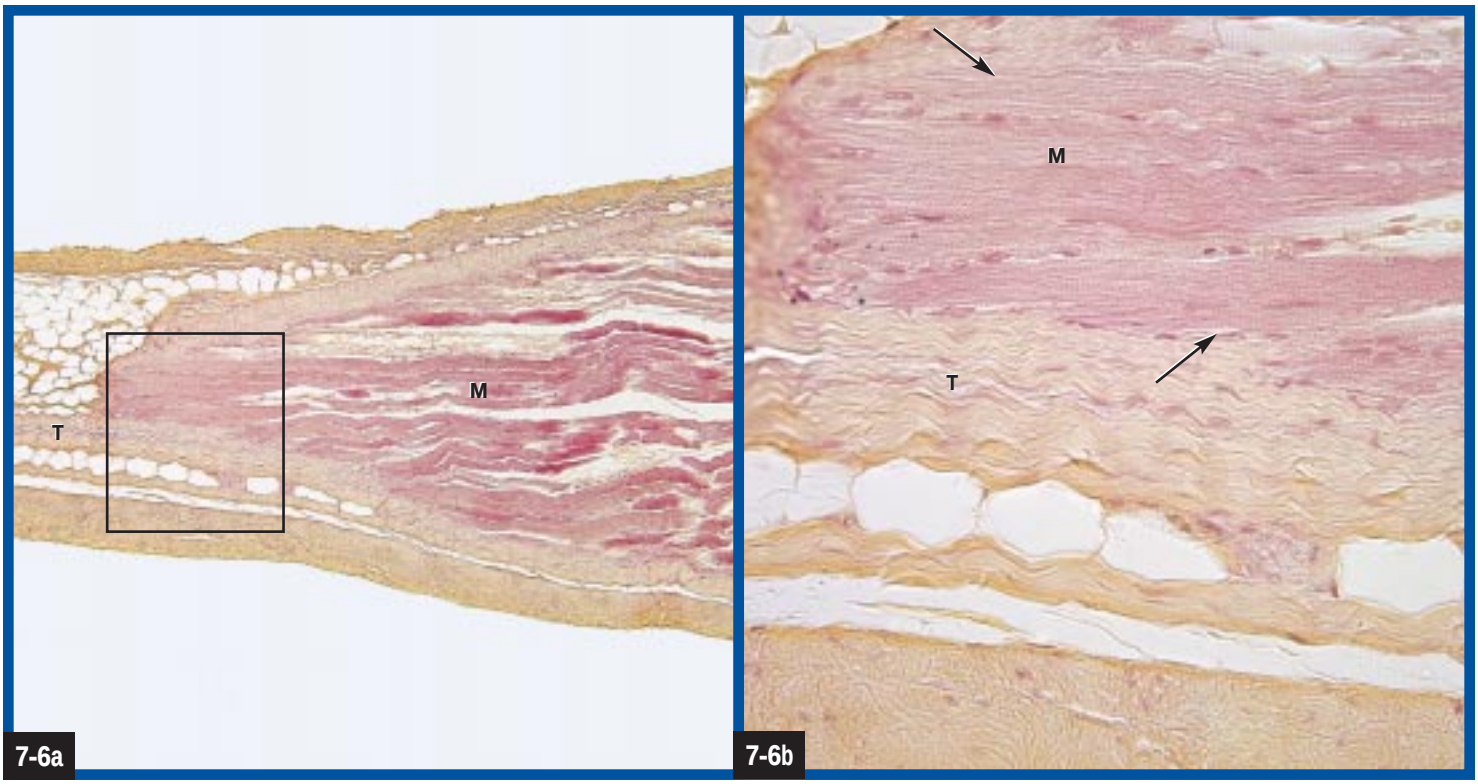


CONNECTIVE TISSUE OF SKELETAL MUSCLES Muscle fibers in a skeletal muscle are held together by fibrous connective tissue. Epimysium (Ep) surrounds the entire muscle, perimysium (P) surrounds a fascicle of fibers, and endomysium (En) surrounds each individual fiber. (a) A thick epimysium is seen in this muscle. *(X250)* (b) The fibers in this specimen have separated during preparation, but this makes the three connective tissue layers more visible and emphasizes their continuity. It also defines the fascicles (outline-F). *(X250)*



MUSCULOTENDINOUS JUNCTION (a) In this micrograph, the end of the muscle (M) and its tendon (T) are seen. *(X60)* (b) In this higher magnification of the boxed region in (a), the continuity of the muscle's connective tissue components combining to form the tendon is visible. Also seen are the connective tissue fibers bound to the muscle fibers' membrane (arrows). *(X250)*

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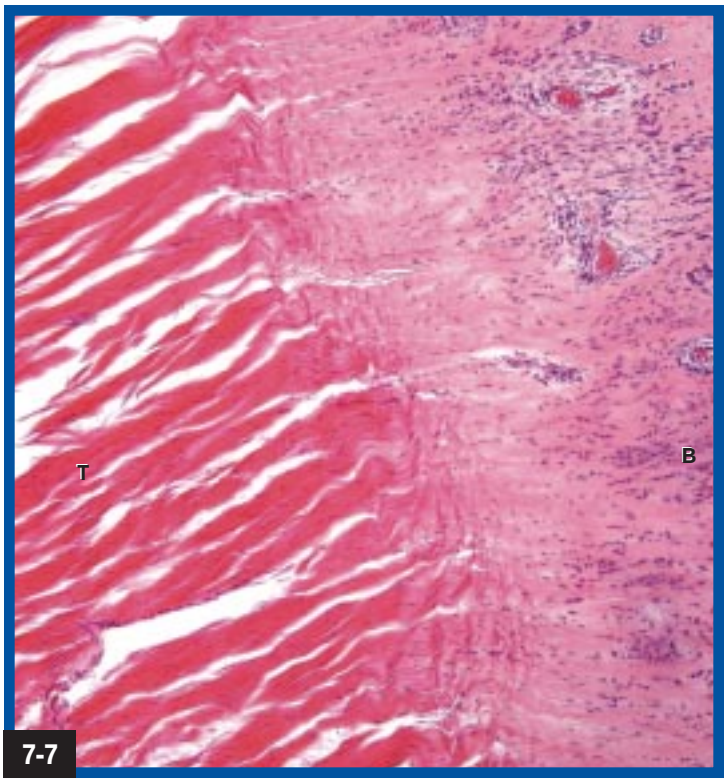
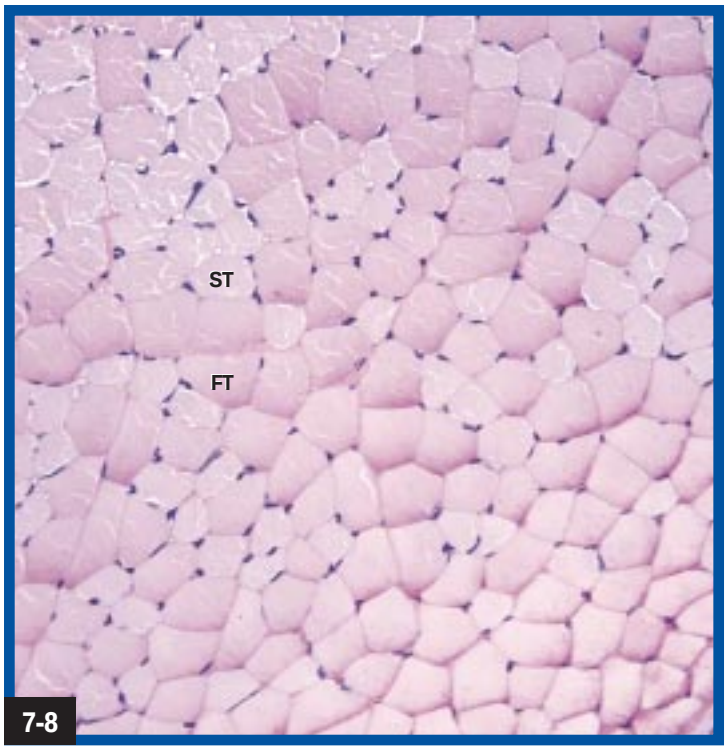
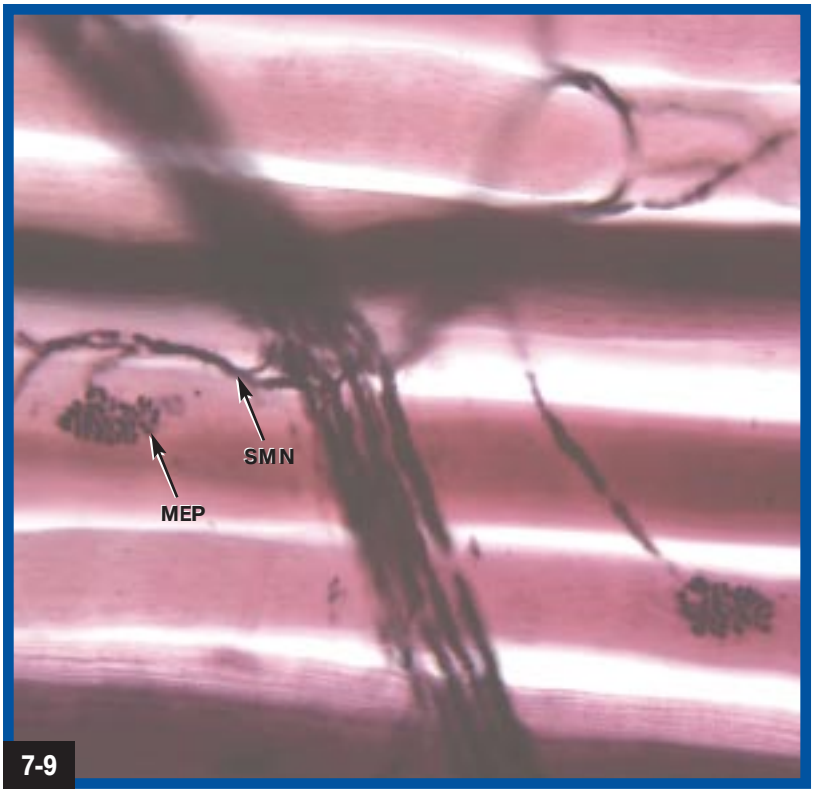


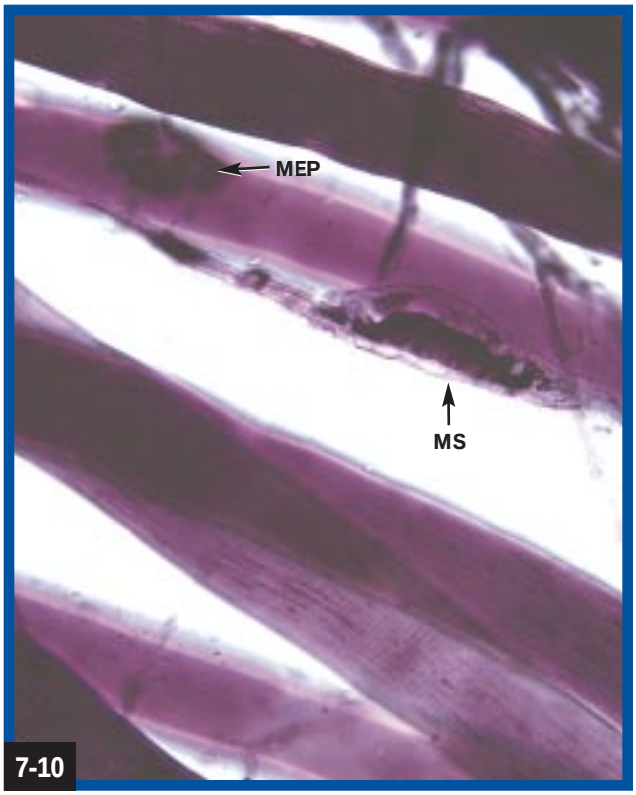
TENDINOUS ATTACHMENT TO BONE The collagenous fibers of the tendon (T) on the left blend with the periosteum and penetrate the bone (B) matrix to anchor the muscle firmly to the bone. *(X60)*



FAST AND SLOW TWITCH FIBERS Two fiber types are identifiable in this micrograph stained for glycogen (PAS reaction), which is more abundant in the larger white fast twitch fibers (FT). The fibers lacking glycogen tend to be the smaller, red slow twitch fibers (ST). (*X250*)



MOTOR END PLATE The junction between a somatic motor neuron (SMN) and its muscle fiber is a complex structure known as a motor end plate (MEP). Two are seen here. Acetylcholine is the neurotransmitter that crosses the synaptic gap. *(X250)*



MUSCLE SPINDLES Muscle spindles (MS) are receptors that provide sensory information about the amount of stretch placed on a muscle. A motor end plate (MEP) is also seen. *(X250)*

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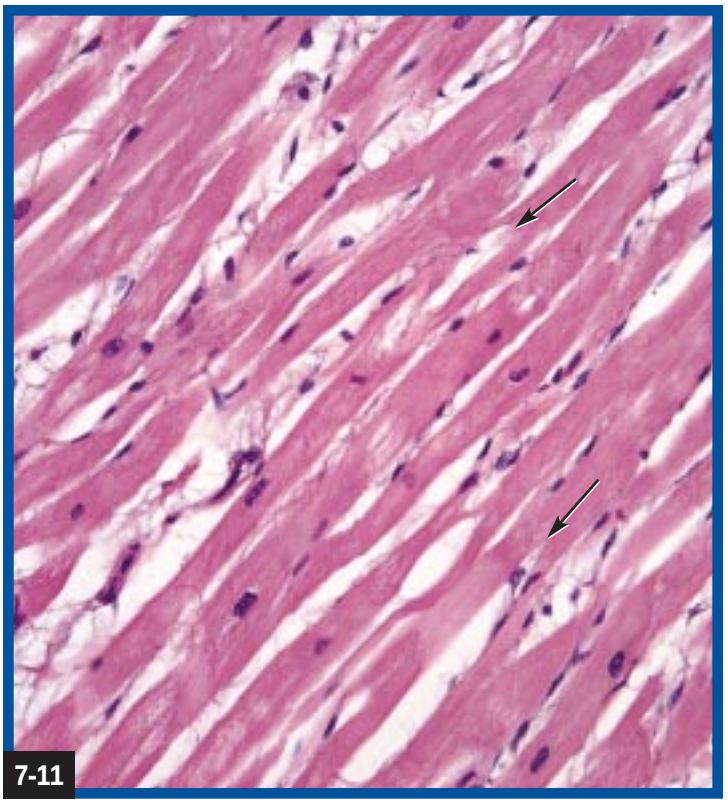
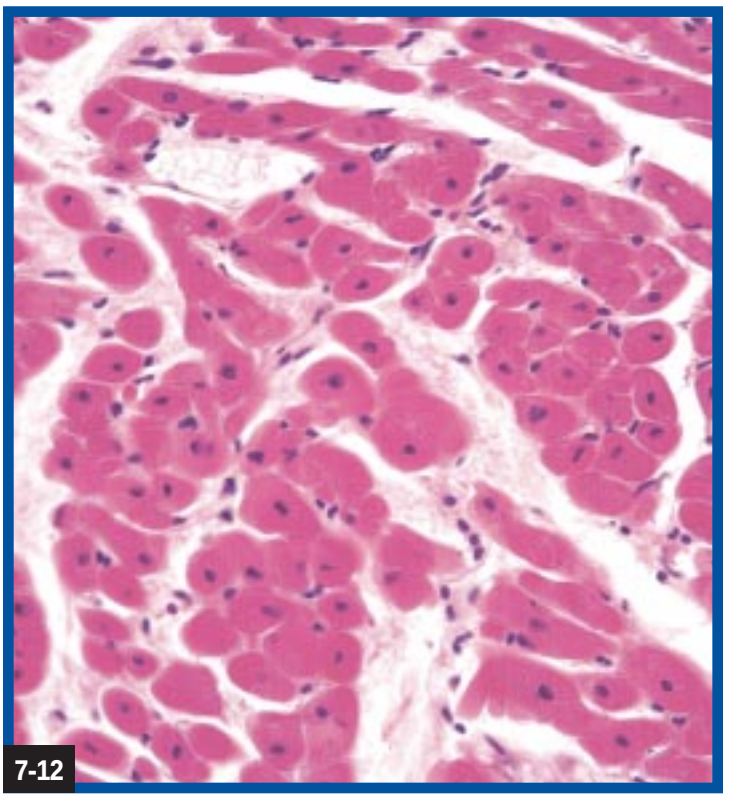


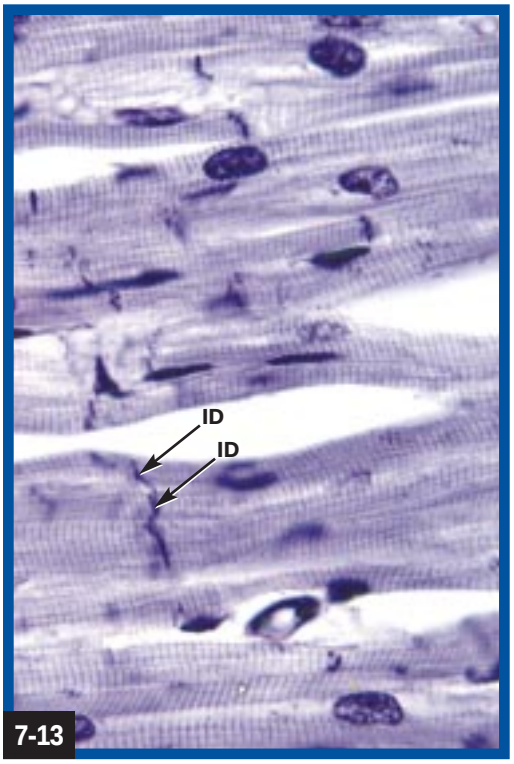
7-11

CARDIAC MUSCLE Cardiac muscle is found only in the heart where it forms the myocardium. Its fibers are faintly striated (not visible in this micrograph), branched (arrows), and uninucleate. *(X250)*



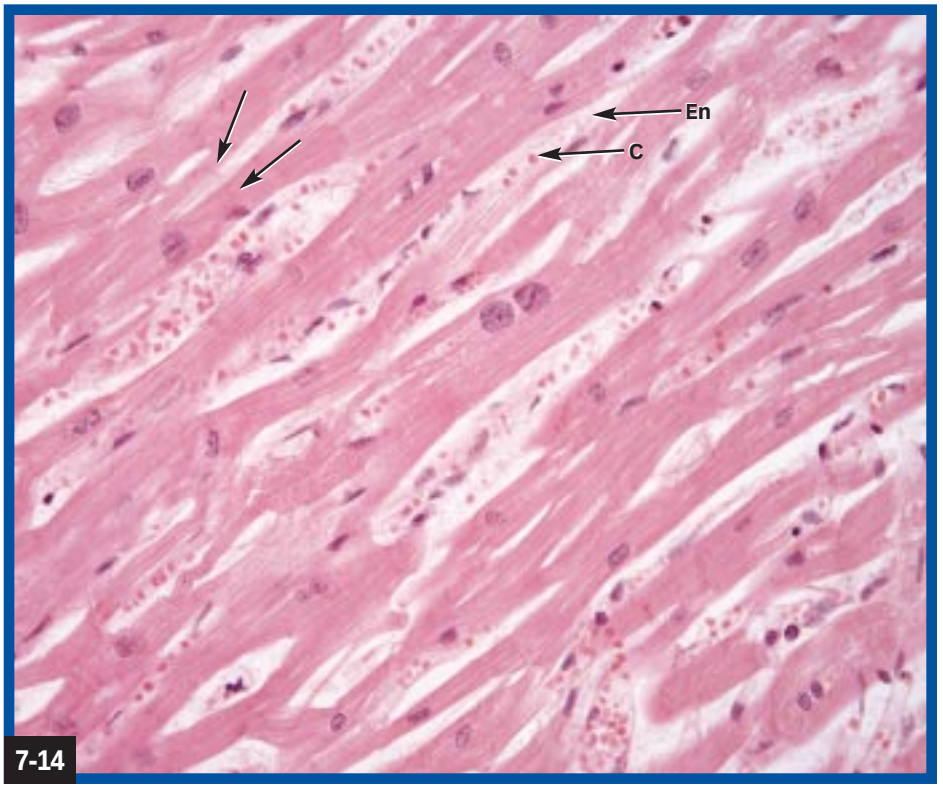
7-12

CARDIAC MUSCLE'S CENTRAL NUCLEI The central position of the nuclei is easily seen in this cross section. *(X250)*



7-13

INTERCALATED DISCS Iron-hematoxylin stain accentuates the striations and intercalated discs (ID) of cardiac muscle fibers. The branching is also visible. *(X630)*



7-14

CAPILLARIES OF CARDIAC MUSCLE Cardiac muscle is very vascular, as evidenced by the numerous capillaries (C) seen in this micrograph. An endomysium (En), faint intercalated discs (arrows), and branching fibers are also visible. *(X250)*

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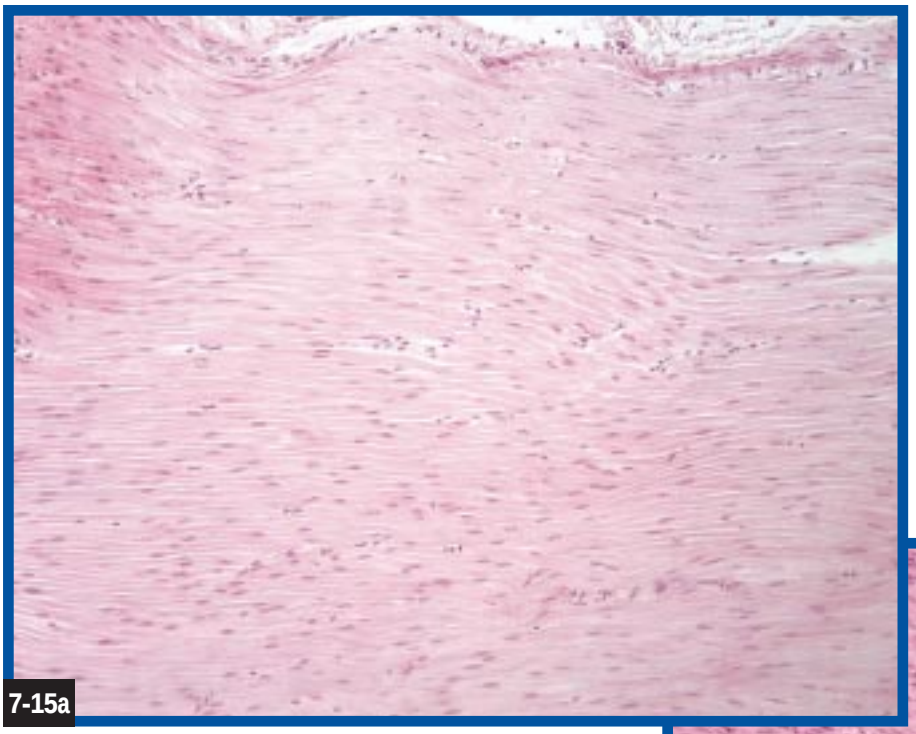

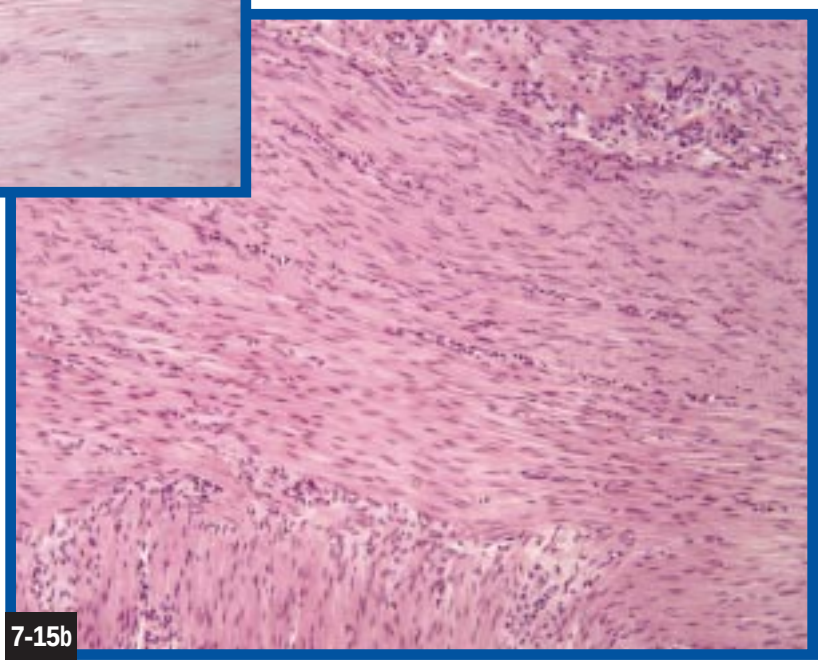

SMOOTH MUSCLE Two specimens of smooth muscle are shown. Note the absence of striations and the random distribution of nuclei throughout the tissue. Smooth muscle is sometimes confused with dense regular connective tissue, but in the latter, nuclei are usually in rows (compare to Figure 4-19). Both specimens were magnified X120.

SMOOTH MUSCLE FIBERS Smooth muscle fibers are elongated with tapered ends. Notice the single nucleus (N) and absence of striations. *(X120)*

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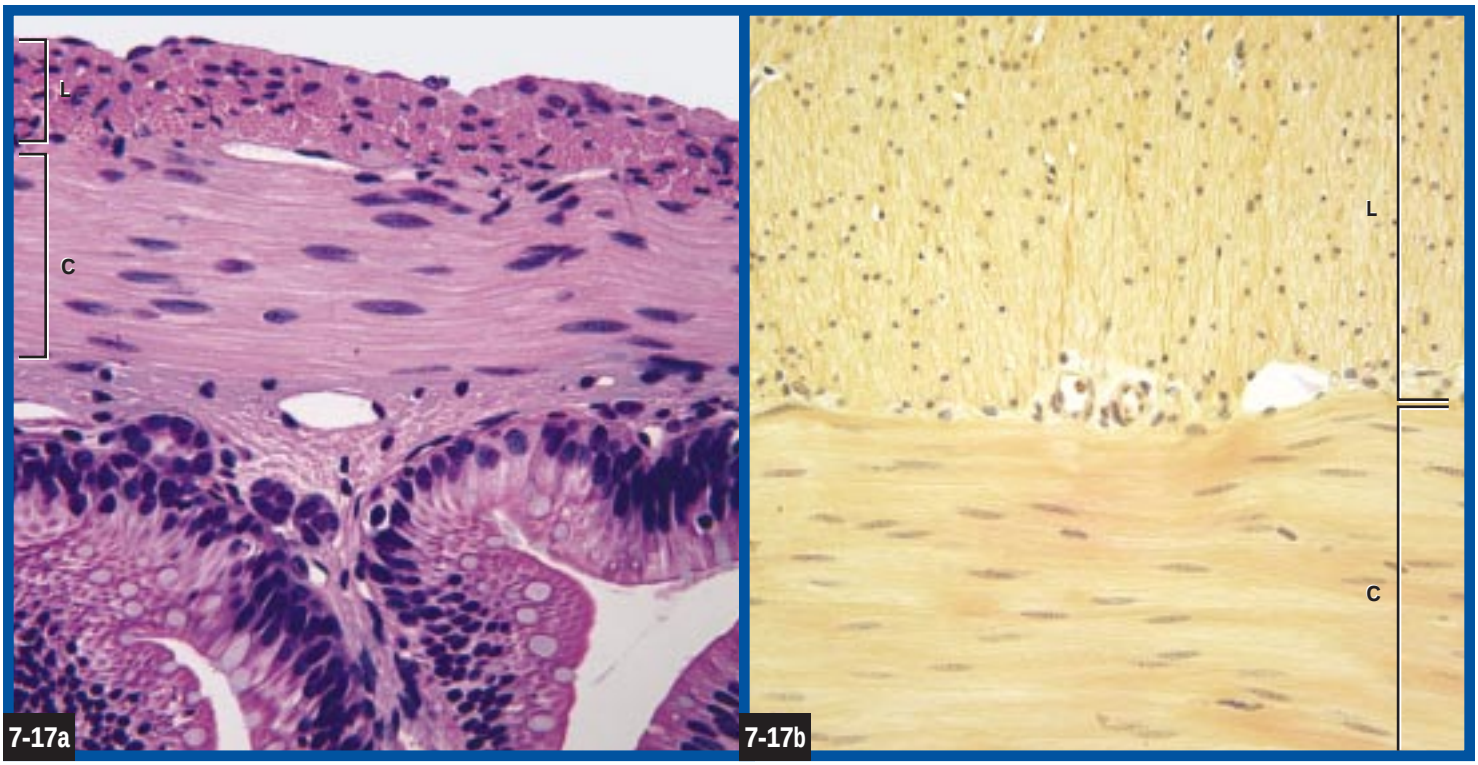

SMOOTH MUSCLE LAYERS In many organs, smooth muscle is found in longitudinal (L) and circular (C) layers, an arrangement that moves materials through the organ by peristalsis. On slides, this allows viewing of smooth muscle in longitudinal and cross sections. (a) Small intestine *(X120)*. (b) Small intestine *(X250)*.

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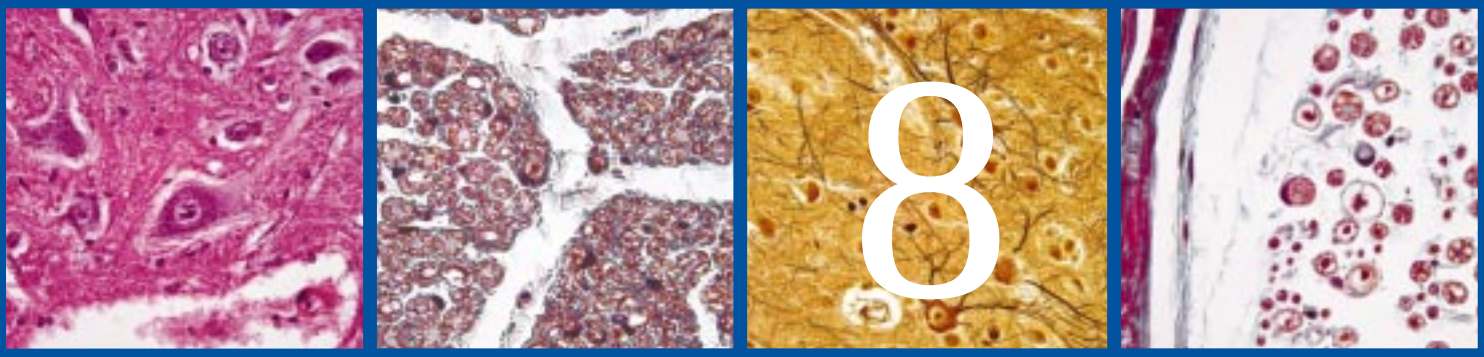
Nervous Tissue and Organs of the Nervous System

CHAPTER

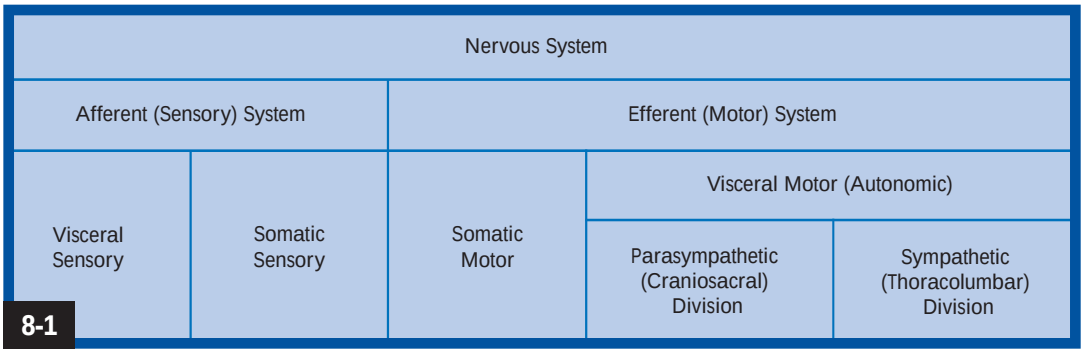


Introduction to Nervous Tissue

Nervous tissue is specialized for coordinating and integrating the activities of body's cells. It accomplishes this through conduction of electrical nerve impulses and secretion of chemical neurotransmitters.

The organs of the nervous system are structurally classified as either being part of the **central nervous system (CNS)**, which includes the brain and spinal cord, or the **peripheral nervous system (PNS)**, which includes nerves, ganglia and sensory receptors.

While it is beyond the scope of this book to provide a detailed description of the nervous system's functional organization, it is necessary to refer to its components (Figure 8-1). For a more detailed description of the role each part fills in the body, the reader is referred to a physiology textbook. Functionally, the nervous system can be divided into two parts: the **afferent (sensory) nervous system**, which carries information toward the CNS or up the spinal cord toward the brain, and the **efferent (motor) nervous system**, which carries information from the brain and away from the CNS. The afferent and efferent systems have **somatic** (relating to the skin and skeletal muscles) and **visceral** (relating to the internal organs) components. The visceral motor system is also known as the **autonomic nervous system**, which is structurally and functionally divided into a **sympathetic (thoracolumbar) division** and a **parasympathetic (craniosacral) division**. The former prepares the body



FUNCTIONAL ORGANIZATION OF THE NERVOUS SYSTEM

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to contend with stressful and life threatening situations, whereas the latter is involved in body maintenance during nonstressful times.

Cells of Nervous Tissue

Nervous tissue is composed of two basic cell types: **neurons**, which are responsible for conduction and integration of nerve impulses, and **neuroglia (glial cells)**, which support neurons (Figure 8-2). The region between cells, the **neuropil**, is a three-dimensional mesh of cellular processes and blood vessels.

Glial Cells

Glial cells do not conduct nerve impulses. Instead, they support neurons and have many functions typically associated with fibrous connective tissues. There are several types, some more easily identified than others. **Microglia** are phagocytic cells of the mononuclear phagocytic system. They are the smallest of the glial cells and have an elongated dark staining nucleus with little cytoplasm. They are difficult to identify with certainty in routine preparations (Figure 8-3). **Astrocytes** (Figure 8-4) are highly branched cells that occupy most of the space between neurons in the CNS. They may be associated with blood vessels and the pia mater (see page 81) by way of **perivascular feet**. In addition to other poorly understood functions, they help form the **blood-brain barrier**. **Protoplasmic** and **fibrous astrocytes** are difficult to differentiate in light micrographs. **Oligodendrocytes** are responsible for producing myelin (see below) in the CNS (Figure 8-5). Each oligodendrocyte may be associated with 50 or more different neurons. They are small cells with a dark cytoplasm and nucleus. They are the most abundant glial cells in white matter. **Schwann cells** are responsible for producing myelin in the PNS (Figure 8-6). **Ependymal cells** line the ventricles and the central canal of the spinal cord (Figure 8-7). They are cuboidal to columnar in shape and join with the pia mater to form the **choroid plexus**, a vascular structure responsible for production of cerebrospinal fluid (CSF). **Satellite cells** (Figure 8-8) are associated with and support neurons in ganglia (see below).

Neurons

Although **neurons** come in a variety of sizes and shapes, they have many features in common (Figure 8-9). The portion of the neuron containing the majority of cytoplasm and the nucleus is called the **cell body** or **perikaryon**. The nucleus often has a prominent nucleolus. The cytoplasm may show an abundance of **neurofibrils** (Figure 8-10) in it or have basophilic granules called **Nissl bodies** (Figure 8-11). The fibrils comprise the cytoskeleton and the Nissl bodies are regions of rough endoplasmic reticulum. A pale cytoplasmic region may be visible near the nucleus. This is the site of a Golgi apparatus.

Extending from the cell body are cytoplasmic processes of two types. **Dendrites** receive impulses and conduct them to the cell body. They are usually short and highly branched. **Axons** transmit the nerve impulse away from the cell body to another neuron, a muscle, or a gland. Axons are up to a meter in length and branch at the end. Depending on the type of neuron, there may be one to many dendrites, but there is always a single axon. Any long, thin neuronal process is called a **nerve fiber**, but usually the term applies to axons.

Neurons can be functionally divided into three groups. **Sensory neurons** carry impulses towards the CNS, whereas **motor neurons** carry impulses away from the CNS. **Interneurons** conduct impulses between sensory and motor neurons within the CNS.

There are three structural types of neurons. These are based on the shape of the cell body and the number and characteristics of the cytoplasmic processes. **Multipolar neurons** (Figure 8-12) have many short dendrites and a single long axon arising from an irregularly shaped cell body. The axon can be identified by the absence of Nissl substance at its base, the **axon hillock**. Motor neurons and interneurons are multipolar. **Bipolar neurons** have a single dendrite and a single axon emerging from opposite ends of the elongated cell body (Figure 8-13). These are not found in many places of the body. Two examples are in the olfactory and optic pathways. **Unipolar (pseudounipolar) neurons** (Figure 8-14) are derived from bipolar neurons. During development, the axon and dendrite fuse near the cell body so that only a single process emerges from it. The "dendrite" ends up being the longer of the two and is called the **peripheral process**. It carries the impulse from a sensory receptor to the cell body. The "axon" becomes the **central process**. It carries the impulse from the cell body to a neuron in the CNS. Most sensory neurons are unipolar.

Myelination

Glial cells support nerve fibers. At the very least, fibers in the PNS are nestled into depressions of Schwann cells. These fibers are said to be **unmyelinated**. Many fibers, however, are covered with an insulating fatty material called **myelin**, and are said to be **myelinated**.

In the PNS, a fiber becomes myelinated when Schwann cells wrap around it several times (Figures 8-15 and 8-16). With each wrap, the cytoplasm is squeezed into the remainder of the cell and the two layers of cytoplasmic membrane are pressed together to form the myelin. (Imagine squeezing toothpaste from the base of the tube toward the opening.) The myelin sheath, then, is actually several double-layers of cytoplasmic membrane wrapped around the fiber. (Imagine wrapping the empty part of the toothpaste tube around a stick several times.) Surrounding the myelin is the portion of the Schwann cell containing the cytoplasm. This is the

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neurilemma. Occasionally, cytoplasm remaining in the layers of myelin is visible as **Schmidt-Lanterman (clefts) lines** (Figure 8-17).

Nodes of Ranvier (Figure 8-18) are gaps between adjacent Schwann cells where the fiber's membrane is exposed. Each myelinated segment is called an **internode** (Figure 8-19). The activities associated with impulse production only occur at the nodes (rather than along the entire length of the fiber) and thus transmission of the impulse is much more rapid in myelinated fibers than in unmyelinated fibers.

In the CNS, myelination is performed by **oligodendrocytes**. Each oligodendrocyte myelinates fifty or more different fibers and, as such, does not surround each fiber with a neurilemma. Nodes of Ranvier and internodes are present in myelinated fibers of the CNS.

Gray and White Matter

Myelin is a fatty material, and has a whitish appearance to it. In fresh preparations, dense collections of myelinated fibers are referred to as **white matter**, whereas unmyelinated fibers and neuron cell bodies comprise **gray matter** (Figure 8-20). These terms are applied to the CNS, but not the PNS.

Nerves and Tracts

Nerve fibers tend to travel together. In the PNS, collections of fibers are identifiable structures called **nerves**. Nerves are either **sensory** (containing only sensory fibers) or **mixed** (a combination of motor and sensory fibers, both somatic and visceral.

Each nerve is associated with collagenous connective tissue similar in arrangement to the connective tissues of muscles (Figures 8-21 and 8-22). On the surface is **epineurium**, a fibrous covering that wraps and supports the nerve, separating it from the surrounding fascia. The **perineurium** is derived from the epineurium. It enters the nerve and forms nerve fiber bundles called **fascicles**. **Endoneurium** is a delicate connective tissue layer derived from perineurium that surrounds each fiber and Schwann cell. This arrangement weaves all the nerve fibers into a structurally sound unit.

In the CNS, fibers with a common origin and a common destination form **tracts** (Figure 8-23). Tracts do not have the connective tissue components of nerves and are difficult to identify because there are no clear boundaries between them. Tracts may either be **ascending** (sensory) or **descending** (motor), but are never mixed.

Ganglia and Nuclei

As with fibers, neuron cell bodies tend to be in groups. Neuron cell bodies in the PNS are found in structures called **ganglia**. **Spinal (dorsal root) ganglia** are located on either side of the vertebral column in association with the dorsal roots of spinal nerves (Figure 8-24). They contain unipolar sensory neuron cell bodies surrounded by **satellite cells**. **Sympathetic (prevertebral) ganglia** (Figure 8-25) are part of the sympathetic trunks on the ventral side of the vertebral column. They contain sympathetic postganglionic neuron cell bodies. The neurons are multipolar with **lipofuchsin granules** (cellular debris) and lack a well-organized layer of satellite cells. Other ganglia are found in association with the viscera and contain autonomic neuron cell bodies (Figure 8-26).

A group of functionally related neurons in the CNS is called a **nucleus**. (Figure 8-27). By definition, nuclei are in the gray matter, but they are less obvious than ganglia because they lack a connective tissue covering that forms an outer boundary. There are many nuclei in the brain, especially in the thalamus and hypothalamus.

Other Neural Structures

Meninges

Connective tissue is absent from the interior of the CNS, but it is covered with three connective tissue layers referred to as **meninges** (Figure 8-28). The innermost, **pia mater**, is a delicate layer of collagen and elastic fibers with a basement membrane. The middle layer, the **arachnoid**, consists of fibrous strands that form a web-like layer continuous with the pia matter. Blood vessels pass through the **subarachnoid space**, as does **cerebrospinal fluid**. The outermost layer is made of dense connective tissue and is called the **dura mater**. It may be visible in spinal cord preparations, but is usually absent from brain specimens since it contributes to the periosteum of the skull and is difficult to remove with the brain.

Choroid Plexus

The ependymal cells of the brain's ventricles associate with pia mater to form highly vascular infoldings called **choroid plexus** (Figure 8-29). These are responsible for producing cerebrospinal fluid, which bathes the CNS and acts as a shock absorber.

Synapse Structure

A **synapse** is the intercellular junction between a neuron and another cell. If the junction is formed with another neuron, it is called an **axodendritic** or **axosomatic junction** (Figure 8-30). If it is formed with a skeletal muscle cell, it is called a **neuromuscular junction** and the structure is called a **motor end plate** (Figure 8-31). The two cells involved in the synapse do not actually contact one another, but rather have a space called the **synaptic cleft** separating them. When the electrical nerve impulse reaches the end of an axon, a chemical **neurotransmitter** is released by the **presynaptic neuron** that diffuses across the synapse to bind with receptors on the **postsynaptic neuron**. The consequence of neurotransmitter binding to the postsynaptic neuron may be stimulation or inhibition, depending on the neuron and the neurotransmitter.

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Organs of the Central Nervous System

Spinal Cord

The **spinal cord** is continuous with the **medulla oblongata** of the brain stem. It is formed as the medulla passes through the foramen magnum at the base of the skull and continues to its own termination even with the second lumbar vertebra. In cross section (Figures 8-32 and 8-33), the white matter surrounds gray matter, which is in the shape of the letter "H". The gray matter is divided into three or four regions, depending on the part of the spinal cord. The **dorsal gray horns** contain interneuron cell bodies and cell bodies of second order sensory neurons that carry impulses to the thalamus. The dorsal horns usually extend to the surface of the cord. **Ventral gray horns** contain somatic motor neuron cell bodies. There is considerable white matter between the ventral horns and the spinal cord's surface. **Lateral gray horns** are found in spinal cord segments T_1 through L_2 and S_2 through S_4. The former contain sympathetic preganglionic neuron cell bodies, whereas the latter contain parasympathetic preganglionic neuron cell bodies. Finally, the **gray commissure** primarily contains axons of interneurons. In the middle of the gray commissure is the **central canal**. It is small, lined with ependymal cells, and carries cerebrospinal fluid.

The white matter of the cord is divided into **dorsal**, **lateral**, and **ventral columns**. The columns carry ascending and descending tracts of fibers, but the precise locations of the tracts are not identifiable due to the absence of connective tissue boundaries.

The **ventral median fissure** is a deep indentation on the ventral side of the cord along the midline. A shallower and narrower **dorsal median sulcus** is on the dorsal side.

Each spinal nerve is connected to the spinal cord by two roots. These are the **dorsal root** and the **ventral root** (Figure 8-34). Even though all spinal nerves are mixed, sensory and motor fibers segregate in the roots. All sensory fibers entering the spinal cord follow the dorsal root and have their cell bodies in the **dorsal root ganglion**, and all motor fibers leave the cord through the ventral root.

Like other parts of the CNS, the spinal cord is covered with meninges. The dura mater of the cord is continuous with the epineurium of the spinal nerve roots (Figure 8-35).

Medulla Oblongata

The **medulla oblongata** (Figure 8-36) is the part of the brain that joins the spinal cord. Its white matter is composed primarily of ascending and descending tracts. The **pyramidal tracts** carry motor fibers arising from the motor cortex of the cerebrum and are visible as the raised **pyramids** on the ventral surface of the medulla. A majority of the fibers in these tracts cross to the opposite side at the **decussation of the pyramids**. These fibers continue down into the cord to synapse with somatic motor neurons in the ventral gray horns. Medullary gray matter includes various nuclei.

Cerebellum

The **cerebellum** is composed of gray matter around white matter and has a prominently convoluted surface (Figure 8-37). The gray matter is the **cerebellar cortex** and consists of a superficial **molecular layer** and a deeper **granular layer**. The molecular layer is composed mostly of unmyelinated fibers and contains few neurons, whereas the granular layer has numerous neurons. At the junction of the two layers is a row of distinctive neurons called **Purkinje cells** whose dendrites project into the molecular layer and whose axons project into the white matter of the cerebellar medulla (Figure 8-38). The cerebellum is involved in coordinating and refining somatic motor activity. As such, it has connections to and from the motor cortex of the cerebrum, and from **proprioceptors** in muscles, tendons and joints.

Cerebral Cortex

The **cerebral cortex** is the layer of gray matter on the surface of the cerebrum. The cortex is highly folded into **sulci** (depressions) and **gyri** (ridges), more commonly referred to as **convolutions**. The cerebrum is the site of higher thought processes and reasoning, as well as the location of neurons responsible for interpreting sensory input to produce various sensations, initiating voluntary motor activity and storing memory.

In most parts of the cerebral cortex, there are six identifiable layers. These are listed below from superficial to deep (Figures 8-39 and 8-40).

- The **molecular layer** is the most superficial layer of the cortex and is adjacent to the pia matter. It consists primarily of neuronal axons and dendrites and scattered glial cells.
- The **outer granular layer** consists of two neuron types: small **pyramidal cells** and **stellate cells**.
- The **pyramidal cell layer** is fairly thick and contains pyramidal cells of increasing size with increasing depth.
- The **inner granular layer** is composed of stellate cells.
- The **ganglionic layer** has large pyramidal cells **(Betz Cells)**, stellate cells, and cells of Martinotti.
- The **multiform cell layer** is the deepest in the cortex. It is characterized by a diverse grouping of neurons.

White matter of the cerebrum is deep to the multiform cell layer of the cortex. It is composed of projection (both ascending and descending), association (within a hemisphere), and commissural (connecting opposite hemispheres) tracts.

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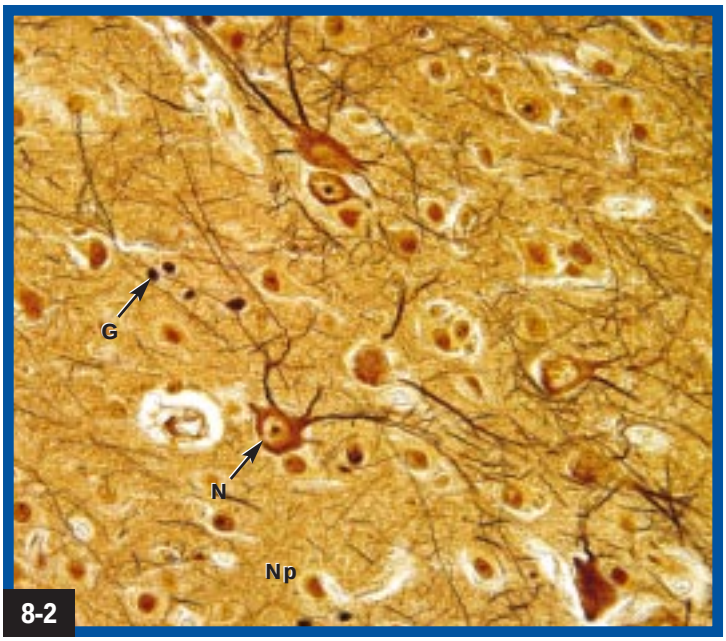
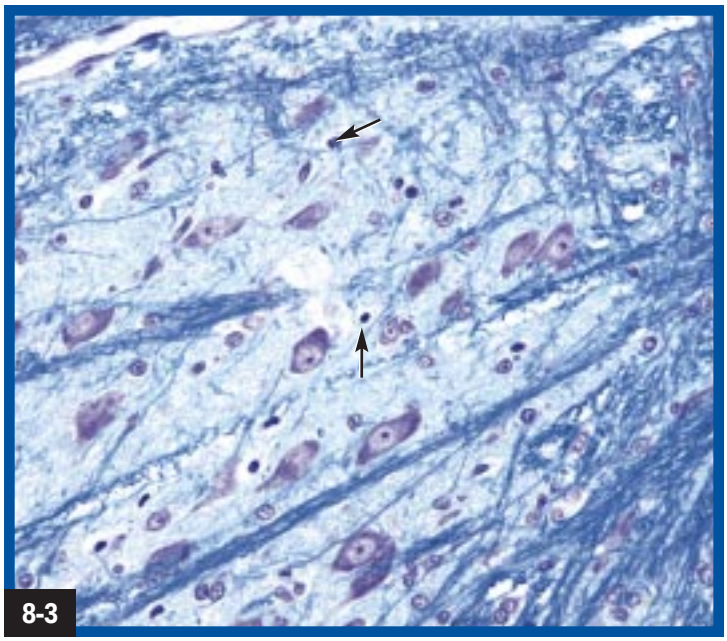
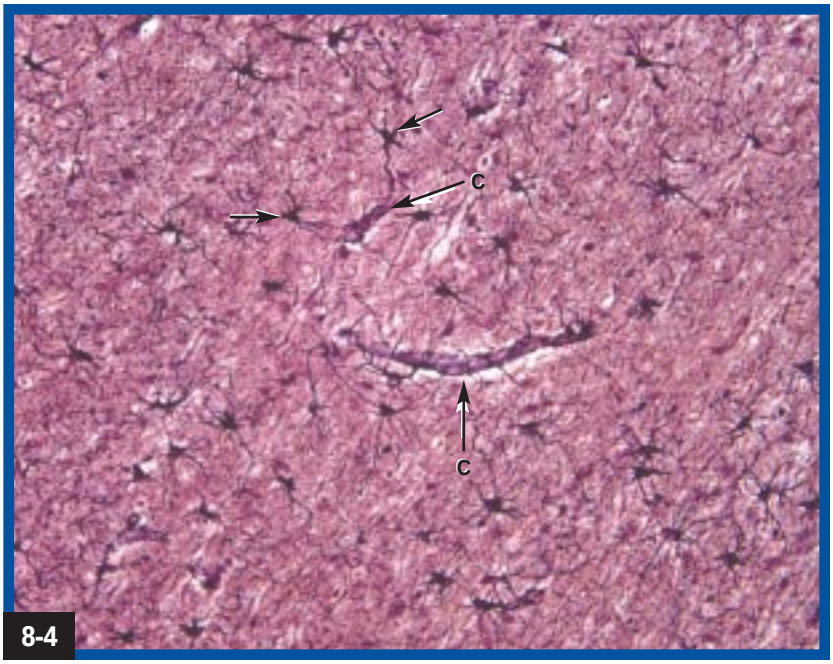


CELLS OF NERVOUS TISSUE Nervous tissue is made of two basic cell types: neurons (N), which are larger and conduct nerve impulses, and smaller neuroglia (glial cells) (G), which perform a variety of functions. Neurons are larger and have a complex shape that generally cannot be fully appreciated in histology specimens because they have been sectioned. The neuropil (Np) primarily consists of neuronal cytoplasmic processes. *(X210)*



PROBABLE MICROGLIA Microglia (arrows) are phagocytic cells of neural tissue, but are difficult to identify with a high degree of certainty in routine preparations. They are small cells with a dense and elongated nucleus. *(X320)*



FIBROUS ASTROCYTES Perivascular feet of astrocytes (arrows) attach to the basement membrane of capillaries (C) to form the blood-brain barrier. (*X210)*

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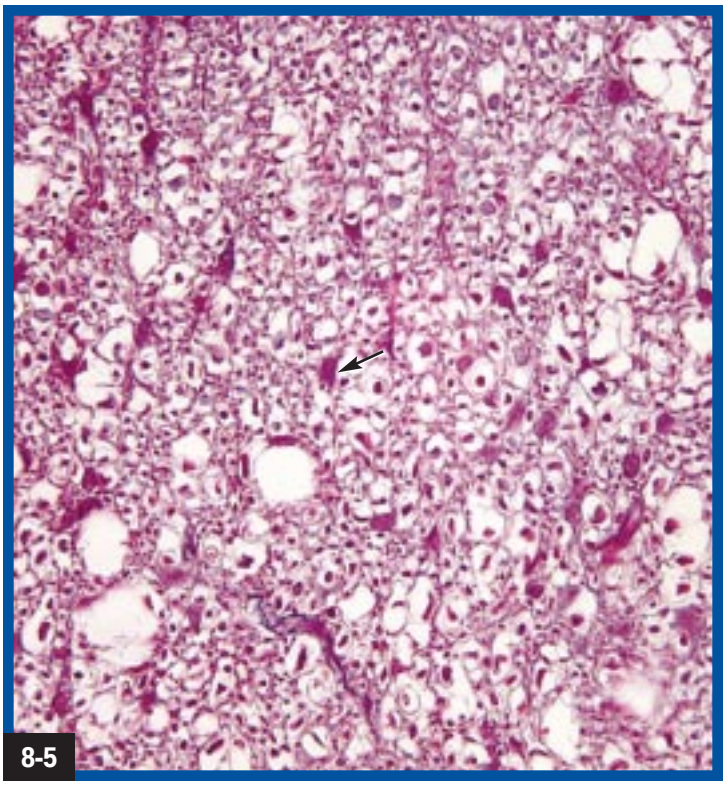
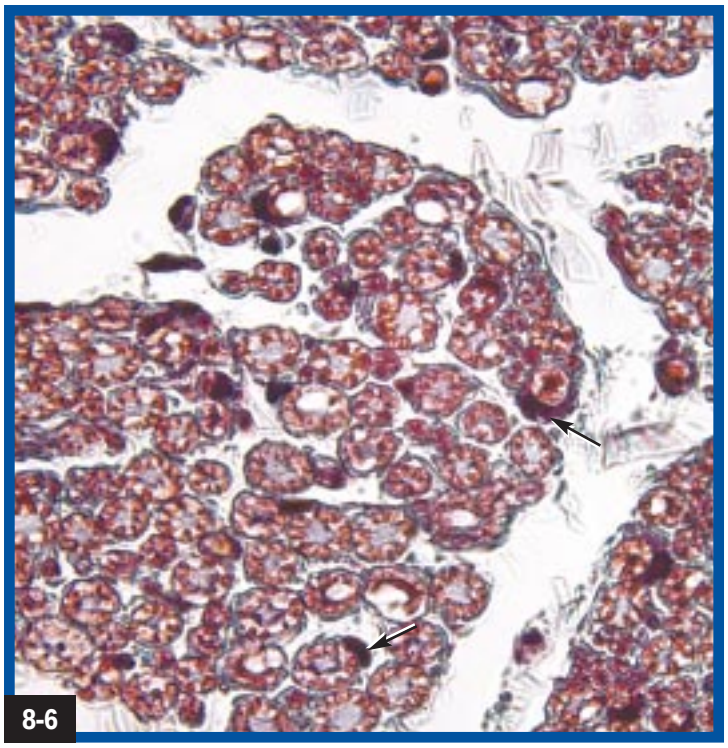


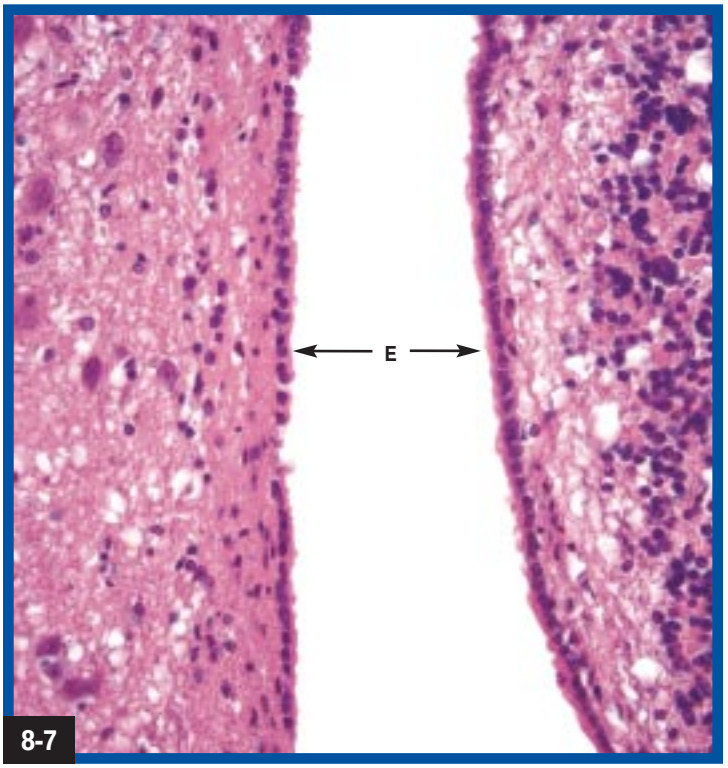
8-5

OLIGODENDROCYTES The most abundant glial cell of white matter is the oligodendrocyte (arrow). These cells are responsible for producing myelin in the CNS. *(X380)*



8-6

SCHWANN CELLS Myelin in the PNS is produced by Schwann cells. In this nerve cross section, the dark staining, crescent shaped Schwann cell nuclei (arrows) are visible in association with a few of the myelinated fibers. *(X630)*



8-7

EPENDYMAL CELLS The ventricular system of the brain is lined with an epithelium-like layer of ependymal cells (E), as seen here. They also are found as part of the choroid plexus, which is responsible for producing cerebrospinal fluid. *(X250)*

8-8

SATELLITE CELLS The neurons of some ganglia are supported by satellite cells (SC). This specimen is from a dorsal root ganglion. *(X250)*

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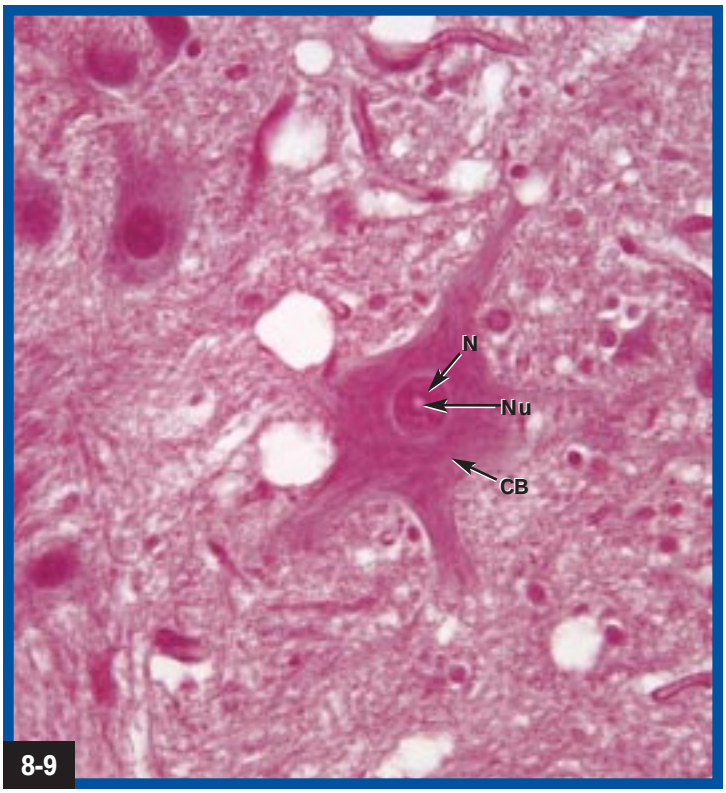
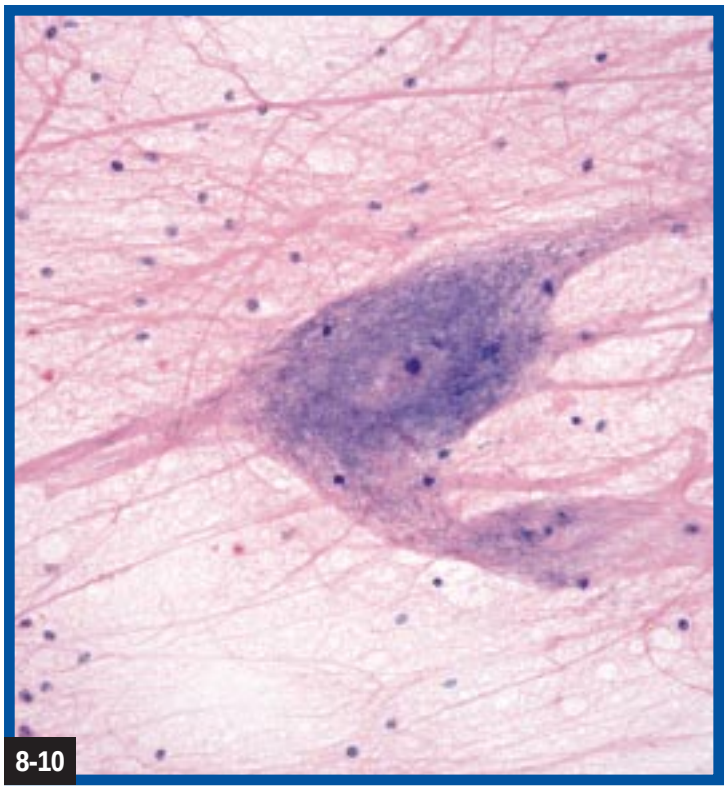
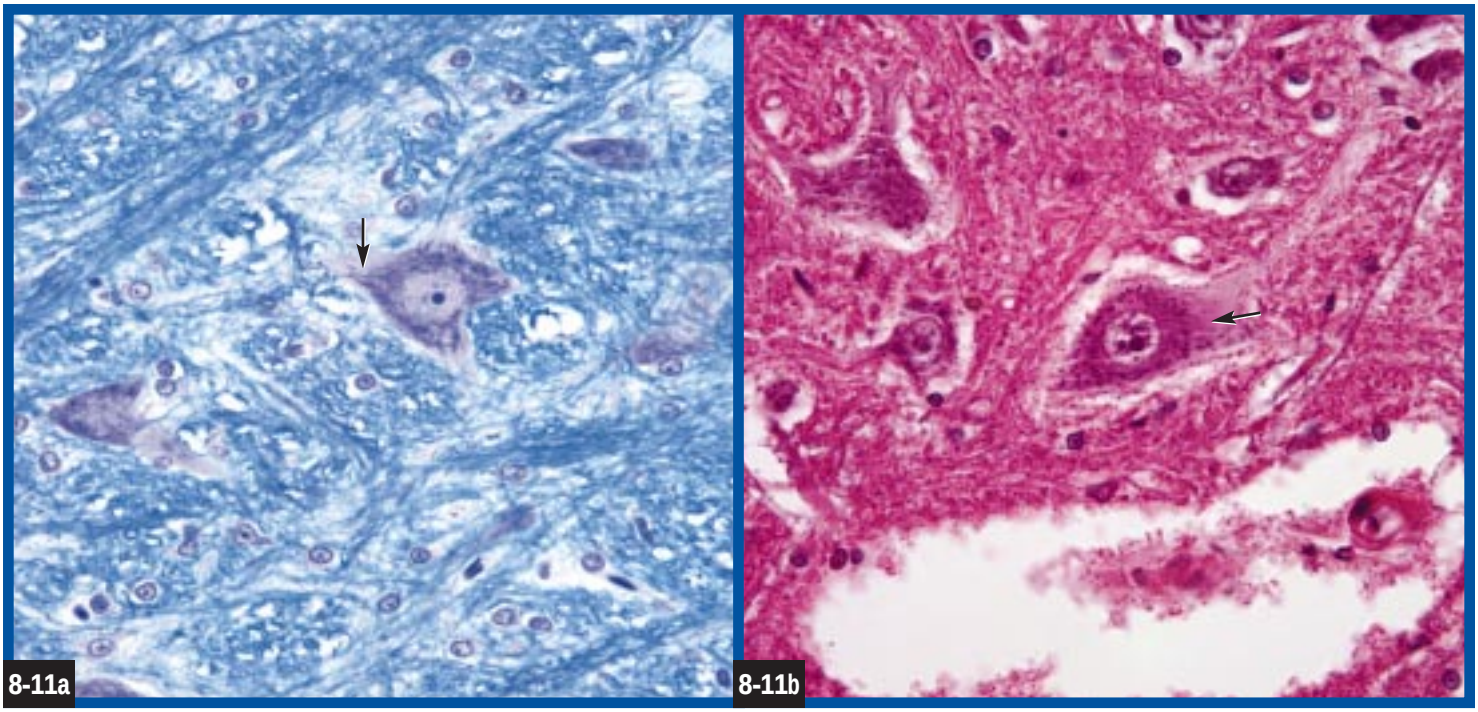


A TYPICAL NEURON Neurons are usually large, irregularly shaped cells. Most have a large nucleus (N) with a prominent nucleolus (Nu). Numerous cytoplasmic processes, called axons and dendrites, extend from the cell body (CB) (perikaryon). The cytoskeleton is visible in this multipolar neuron. *(X250)*



NEUROFIBRILS The cytoskeleton of neurofibrils (blue lines) is often visible in neurons. Notice the large nucleus with its nucleolus. This specimen is a whole mount of neural tissue. *(X250)*



NISSL BODIES IN NEURONS With proper staining, Nissl bodies are visible in the cytoplasm of some neurons. Electron micrographic studies have shown the Nissl substance to be rough endoplasmic reticulum. The Nissl substance is absent from the base of the axon, the axon hillock, making it possible to identify the axon without seeing its entire length (arrows). Both specimens are multipolar neurons. *(X380)*

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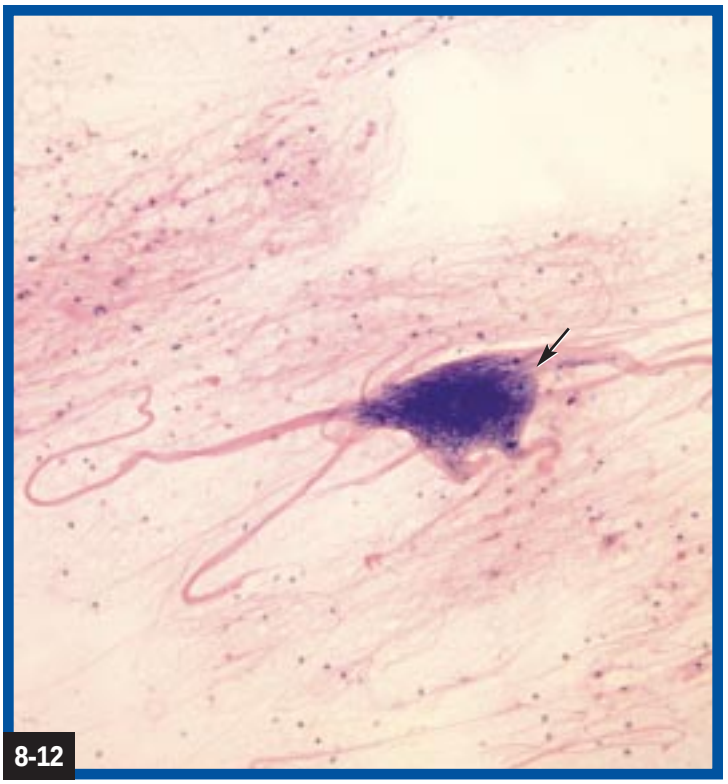
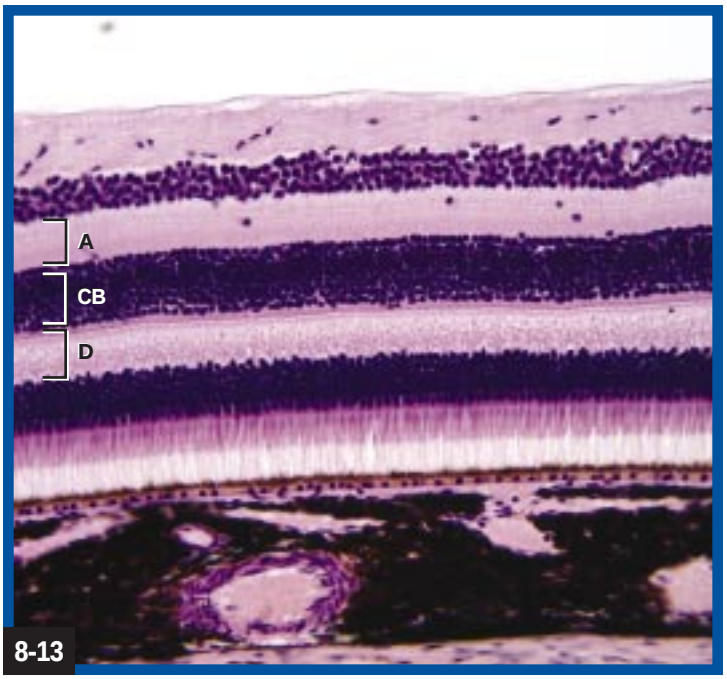


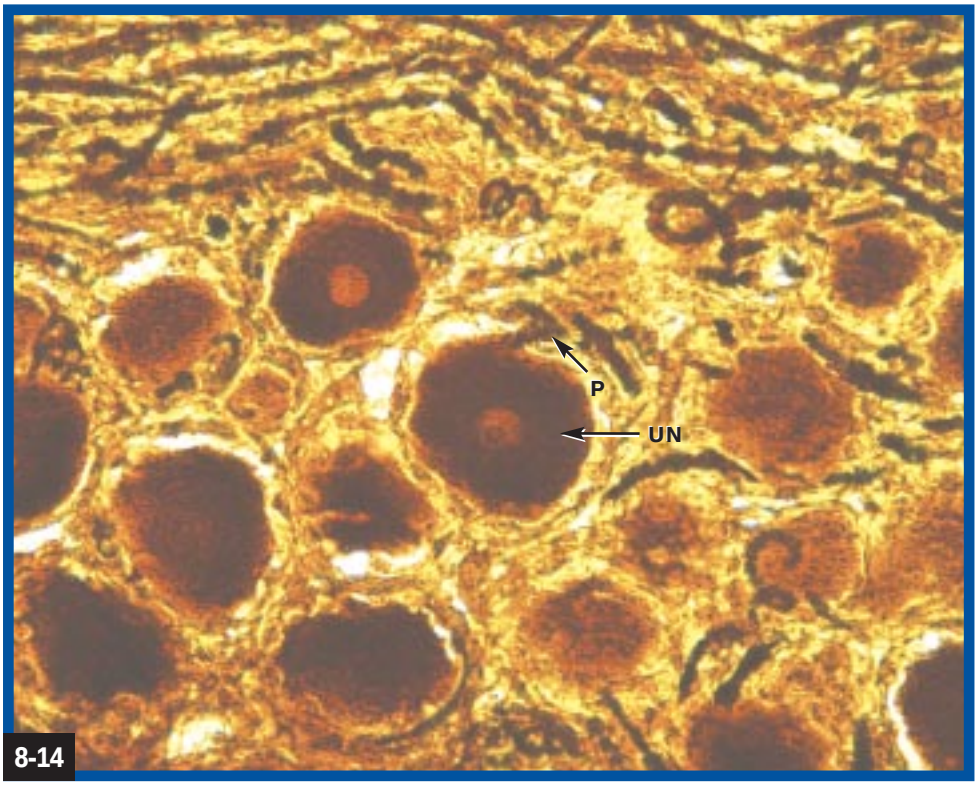
8-12

MULTIPOLAR NEURON This is a smear of neural tissue. Notice the multiple cytoplasmic processes of this neuron and its cytoskeleton of blue neurofibrils. The arrow indicates the axon. *(X100)*



8-13

BIPOLAR NEURONS OF THE RETINA Bipolar neurons have a single axon and dendrite. Their cell bodies are in the layer labeled "CB" with the axons (A) and dendrites (D) extending into the layers on either side. They are found in the retina and a couple of other places in the body. *(X100)*



8-14

UNIPOLAR (PSEUDOUNIPOLAR) NEURONS Unipolar neurons (UN) have a single process (P) that divides into a peripheral process, which comes from a sensory receptor, and a central process, which leads to the CNS. The cell body is spherical. This specimen was taken from a dorsal root ganglion. *(X320)*

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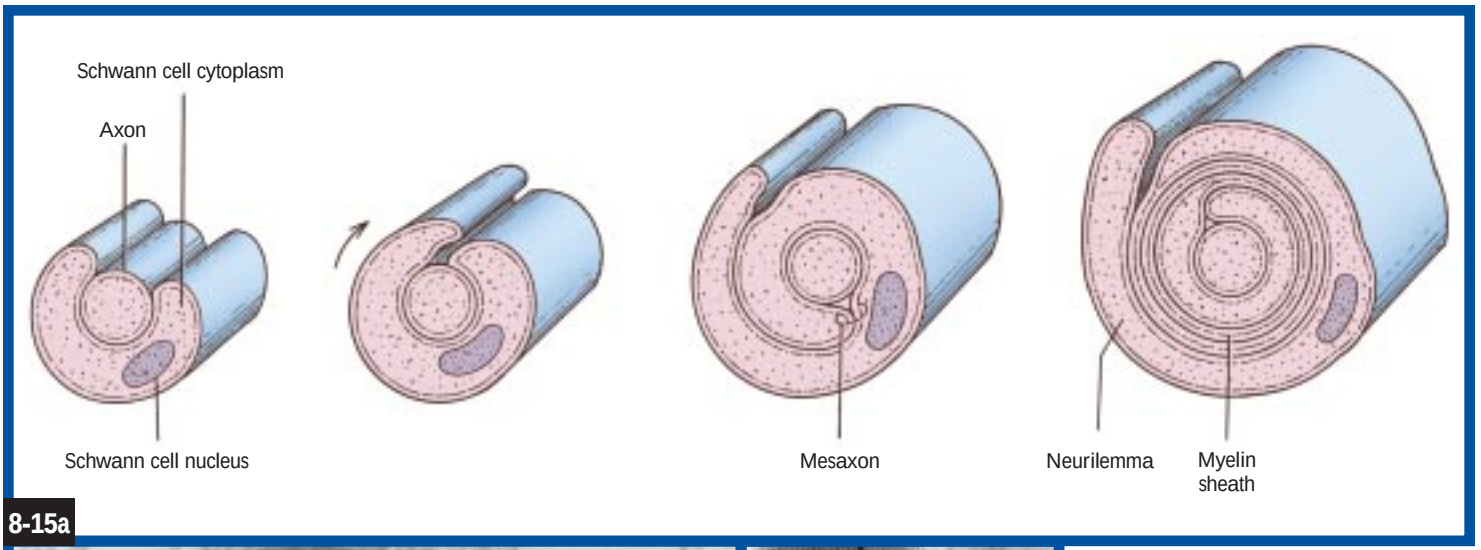

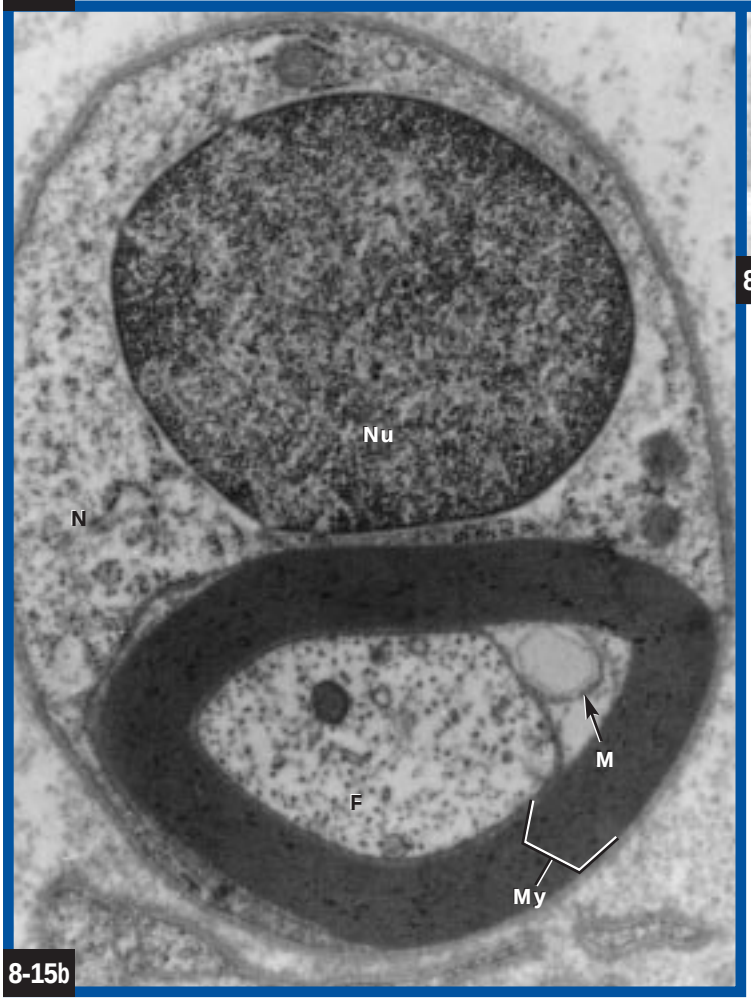

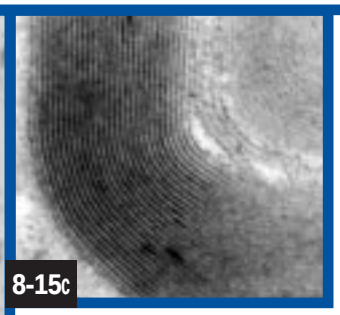

MYELIN SHEATH (a) Myelin is produced by compressed cytoplasmic membrane of a Schwann cell as it wraps around a nerve fiber. (b) This electron micrograph shows the myelin sheath (My) as multiple wraps of the Schwann cell membrane. The mesaxon (M), neurilemma (N), Schwann cell nucleus (Nu), and nerve fiber (F) are also visible. (*X15,000*) (c) The layers of membrane are visible in this higher magnification of myelin. (*X18,750*)

(Micrographs courtesy of UCSD Medical Center.)

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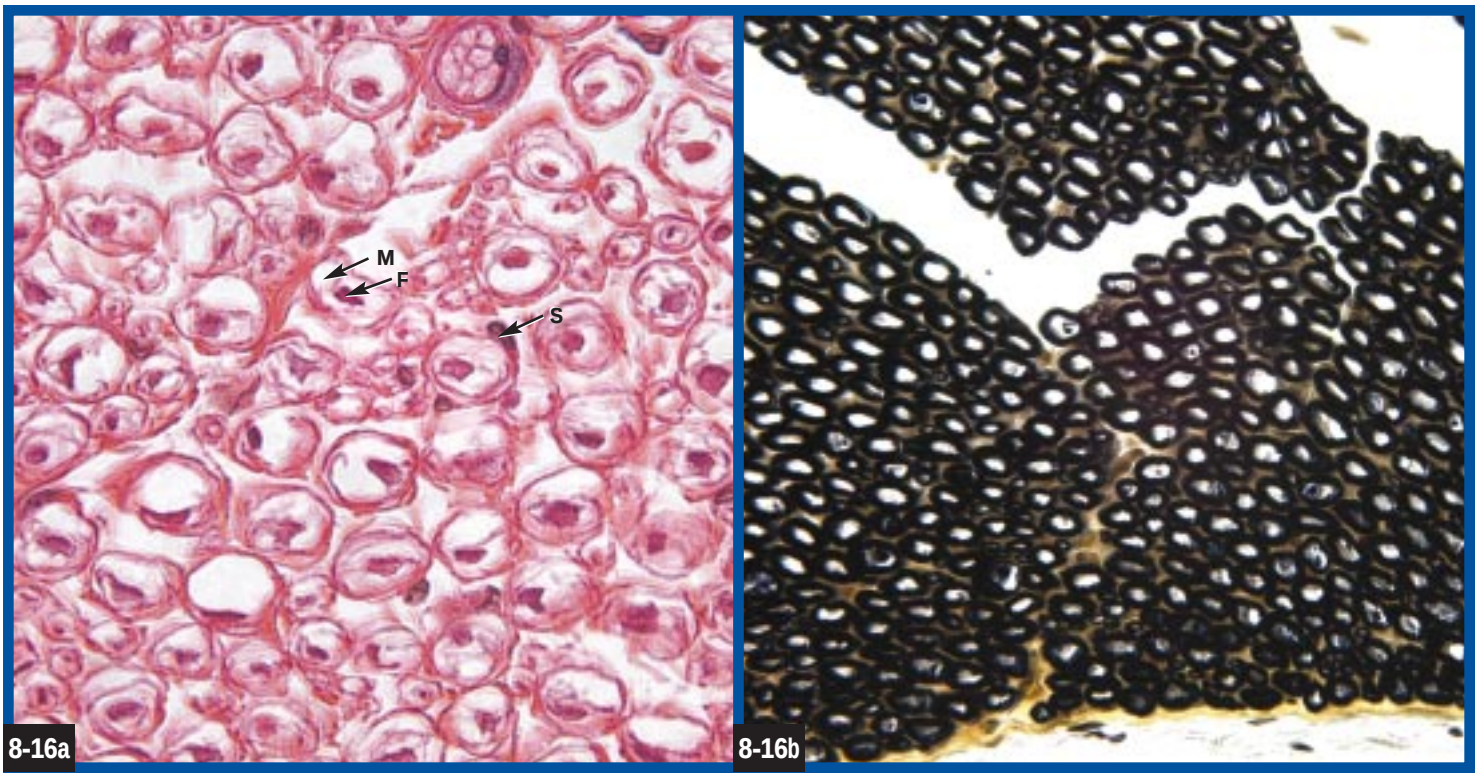
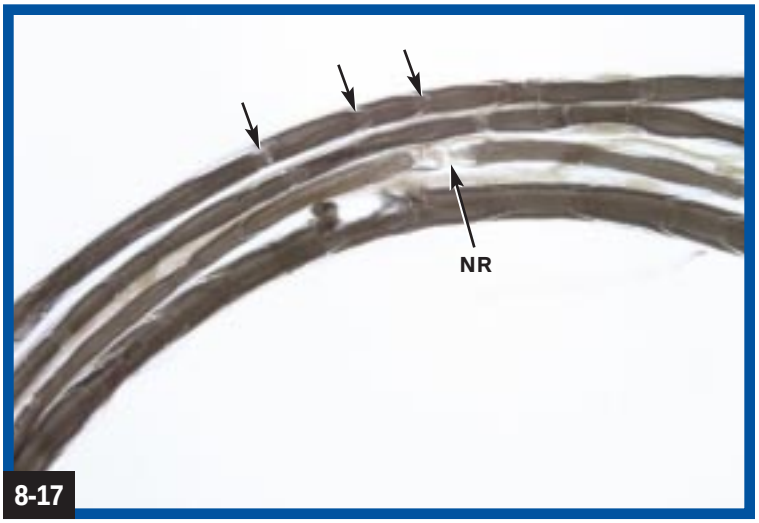
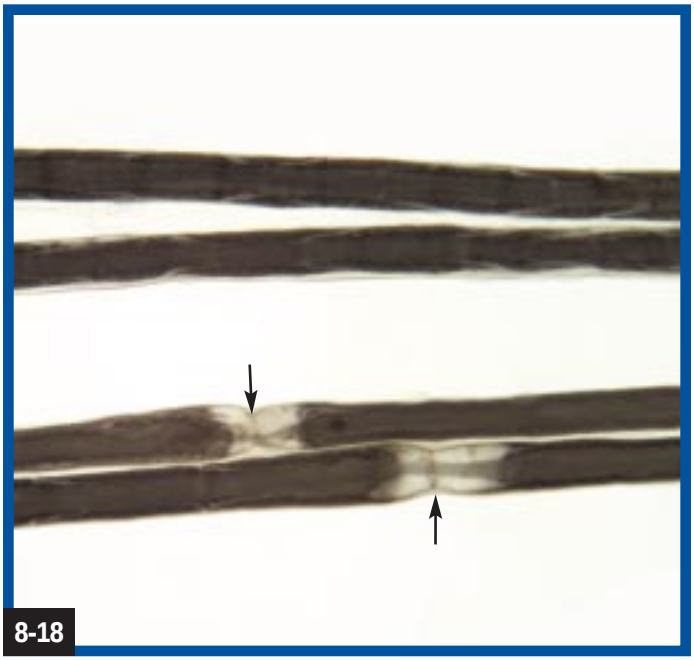


MYELINATED FIBERS (a) In this nerve cross section, the myelin sheaths (M) surround nerve fibers (F), but are disrupted due to slide preparation. Schwann cell nuclei (S) are also visible. (*X630*) (b) This nerve cross section was prepared with an osmium stain that stains fat black and thus highlights the myelin. *(X380)*



SCHMIDT-LANTERMAN CLEFTS During myelination, some cytoplasm is trapped in the myelin sheath and is visible as Schmidt-Lanterman clefts. A node of Ranvier (NR) is also visible. *(X250)*



NODES OF RANVIER Gaps in the myelin sheath between adjacent Schwann cells are called nodes of Ranvier. The electrical activity associated with impulse transmission only occurs at the nodes of a myelinated fiber rather than its entire length, as in unmyelinated fibers. This results in faster impulse conduction. The fiber is visible as a gray line crossing the node. *(X380)*

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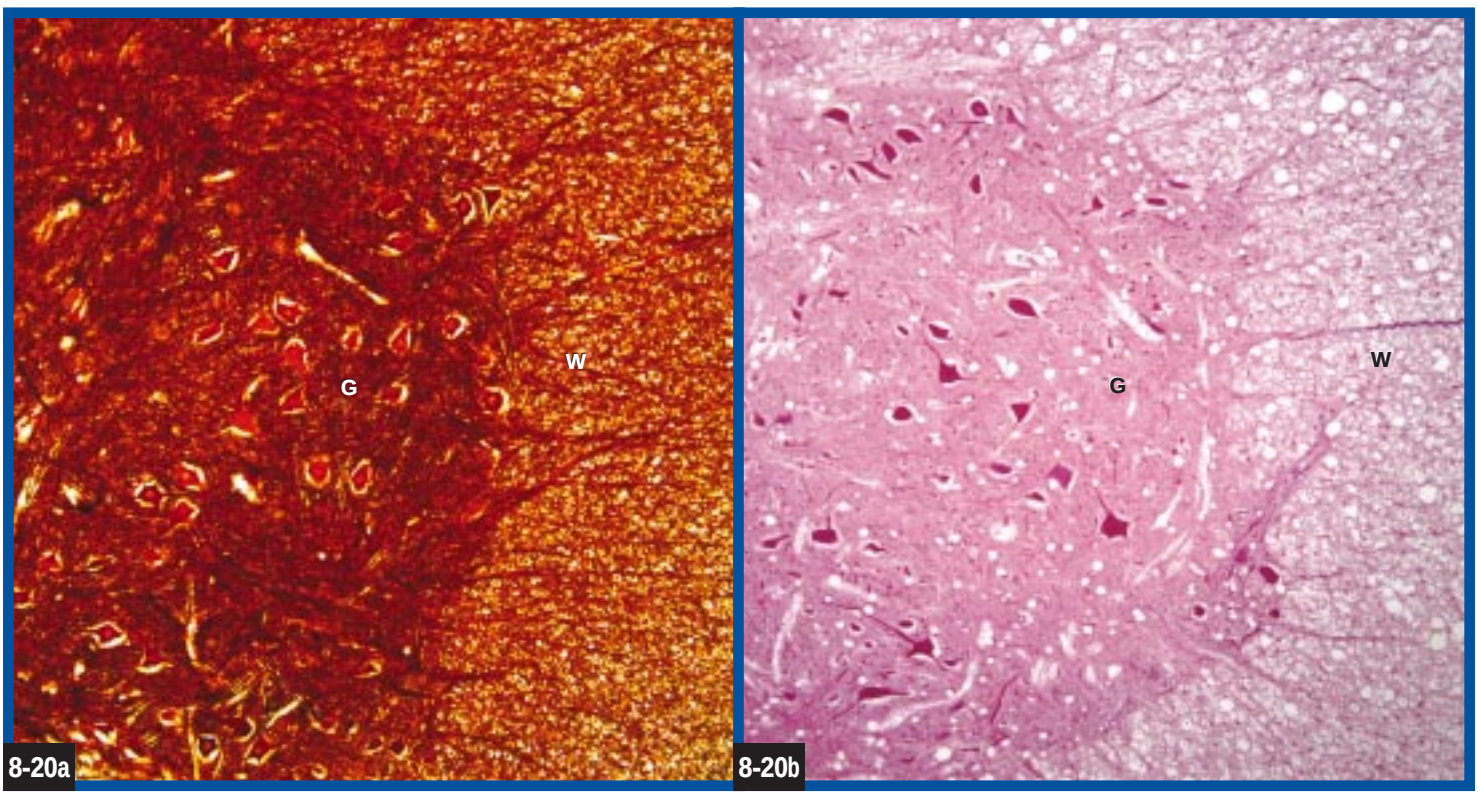
INTERNODES Two nodes of Ranvier are indicated with arrows; the region in between is known as the internode. Since internodes are not involved in impulse transmission and they constitute the majority of the fiber, impulse transmission is more rapid in myelinated fibers than in unmyelinated ones. *(X60)*



GRAY AND WHITE MATTER In the CNS, regions of myelinated fibers have a whitish appearance and are known as white matter (W). The main cells of white matter are oligodendrocytes. Gray matter (G) is composed of neuron cell bodies, glial cells and unmyelinated fibers (though a few myelinated fibers may be found). Both specimens are from the spinal cord. (a) Silver stain, X50. (b) H&E stain, X50.

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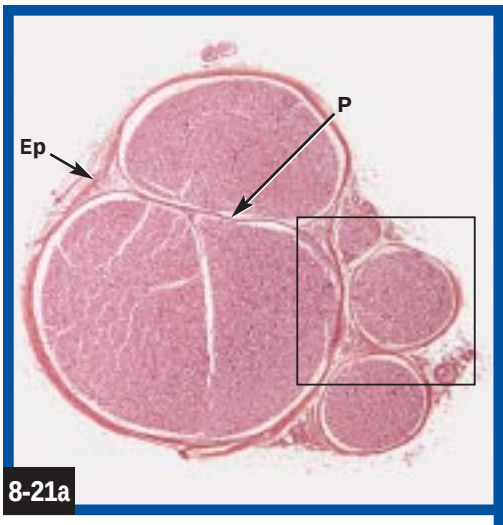

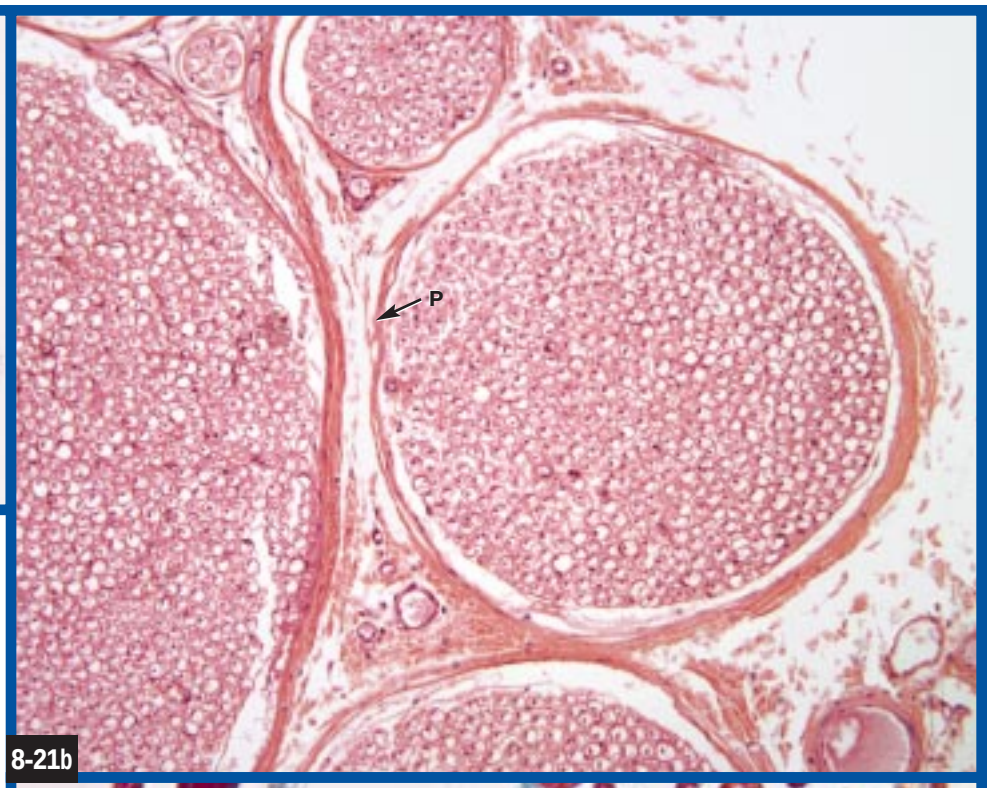

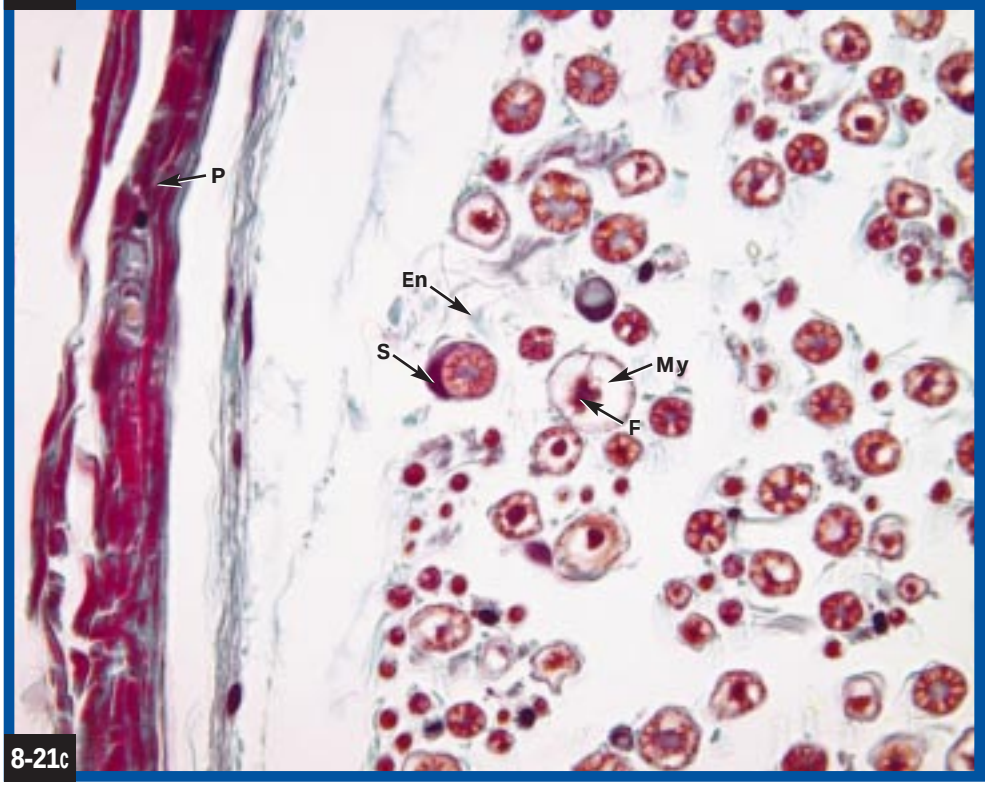

Connective Tissue Components of a Nerve Nerves are made of nerve fibers and connective tissue. Each nerve is surrounded by a connective tissue epineurium (Ep). The perineurium (P) surrounds fascicles of fibers, and the endoneurium (En) surrounds each individual fiber. (a) This is a cross section of a small nerve. (H&E stain, X25). (b) This is an enlargement of the boxed area in (a). (*X125*) (c) This section of a nerve was stained with Masson stain, which makes connective tissue blue. The endoneurium and part of the perineurium is visible. Also seen are Schwann cells (S), myelin (My) and fibers (F). *(X1000)*

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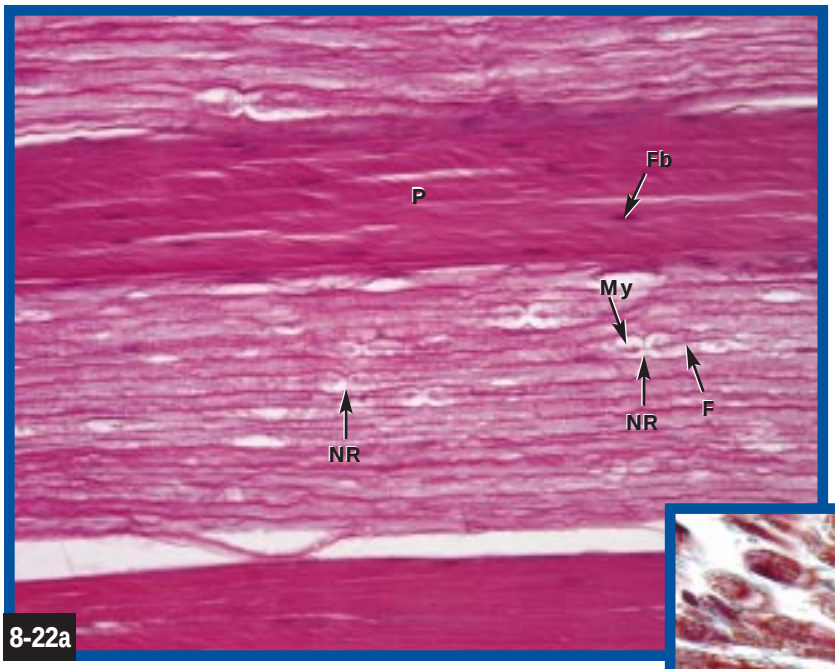
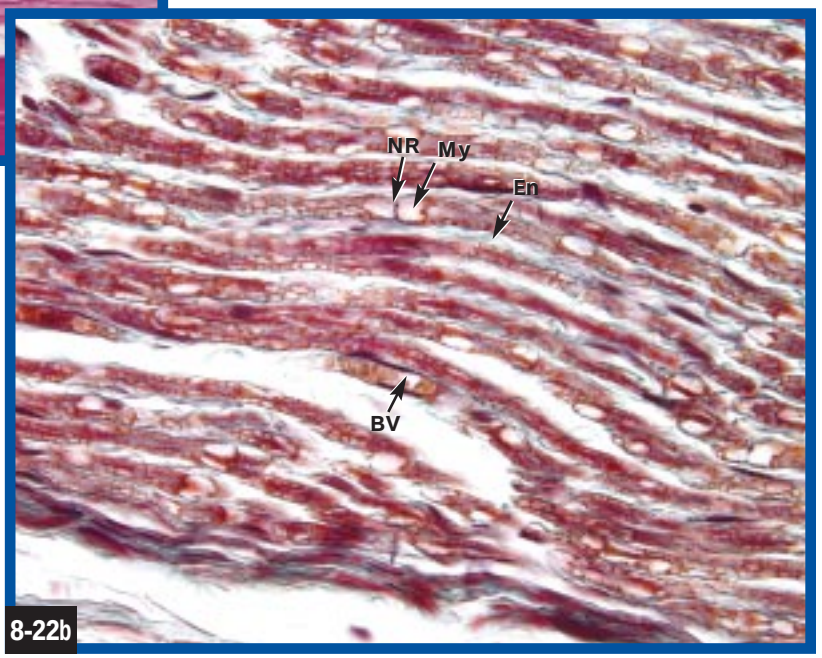
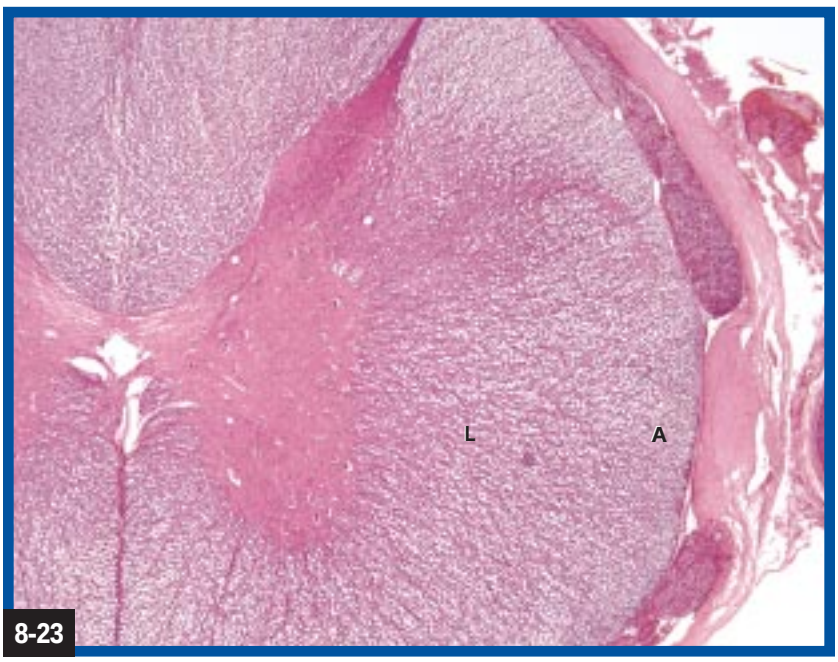


8-22a



8-22b

LONGITUDINAL SECTIONS OF A NERVE (a) The perineurium (P) with fibroblast nuclei (Fb) is obvious, but the endoneurium is difficult to discern in this H&E preparation of a nerve cut in longitudinal section. Myelin (My), nerve fibers (F) and nodes of Ranvier (NR) are also visible. (*X210*) (b) This longitudinal section of a nerve clearly illustrates the endoneurium (En). A blood vessel (BV) is also visible. Other structures are labeled as in (a). *(X320)*



8-23

TRACTS Collections of nerve fibers in the CNS are called tracts and they comprise the white matter. While the general location of each tract is known, their precise boundaries are unclear due to the absence of connective tissue or any other landmark around them. For instance, in this spinal cord specimen the lateral (L) spinothalamic and anterior (A) spinocerebellar tracts are adjacent, but there is no clear boundary between them. (*X20*)

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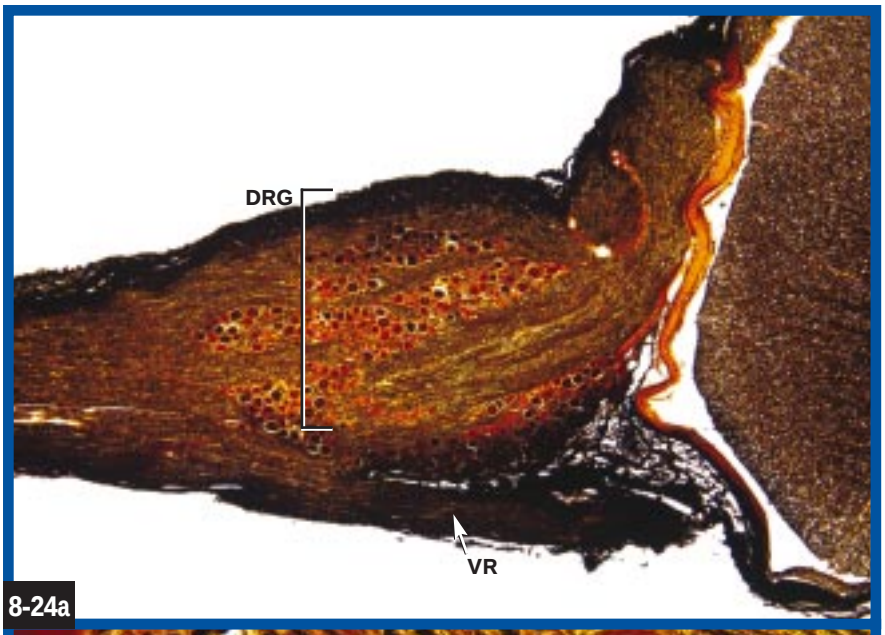
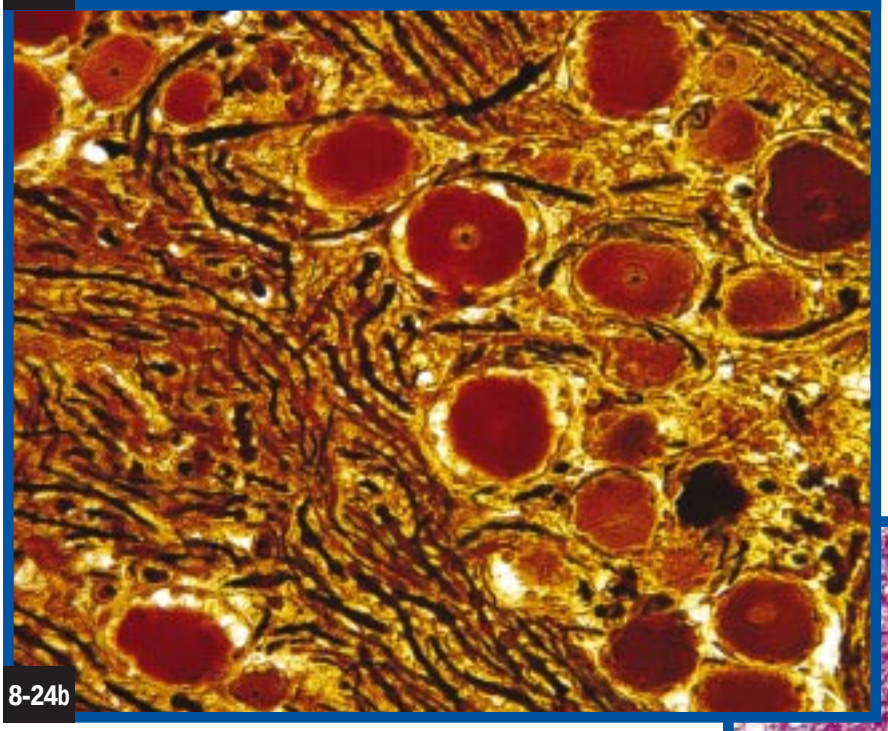
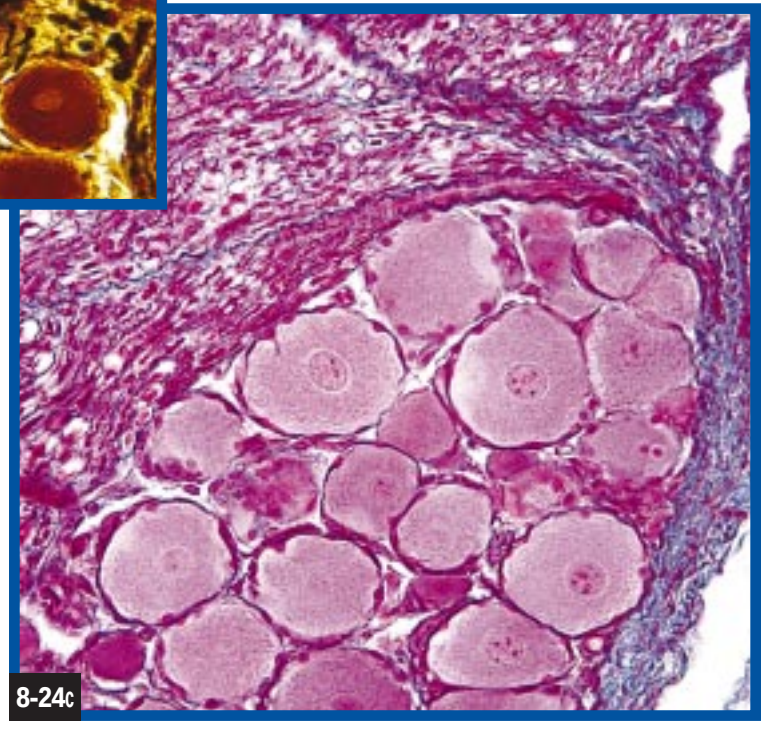


8-24a



8-24b



8-24c

DORSAL ROOT GANGLION Neuron cell bodies in the PNS are found in ganglia. Shown here are three examples of dorsal root ganglia, that are located in the dorsal roots of each spinal nerve and contain sensory neuron cell bodies. (a) The dorsal root ganglion (DRG) is seen as an expanded region of the dorsal root. The ventral root (VR) is also visible. It contains motor fibers. (*X25*) (b and c) The unipolar neuron cell bodies and satellite cells surrounding them are seen in these micrographs. *(X230)*

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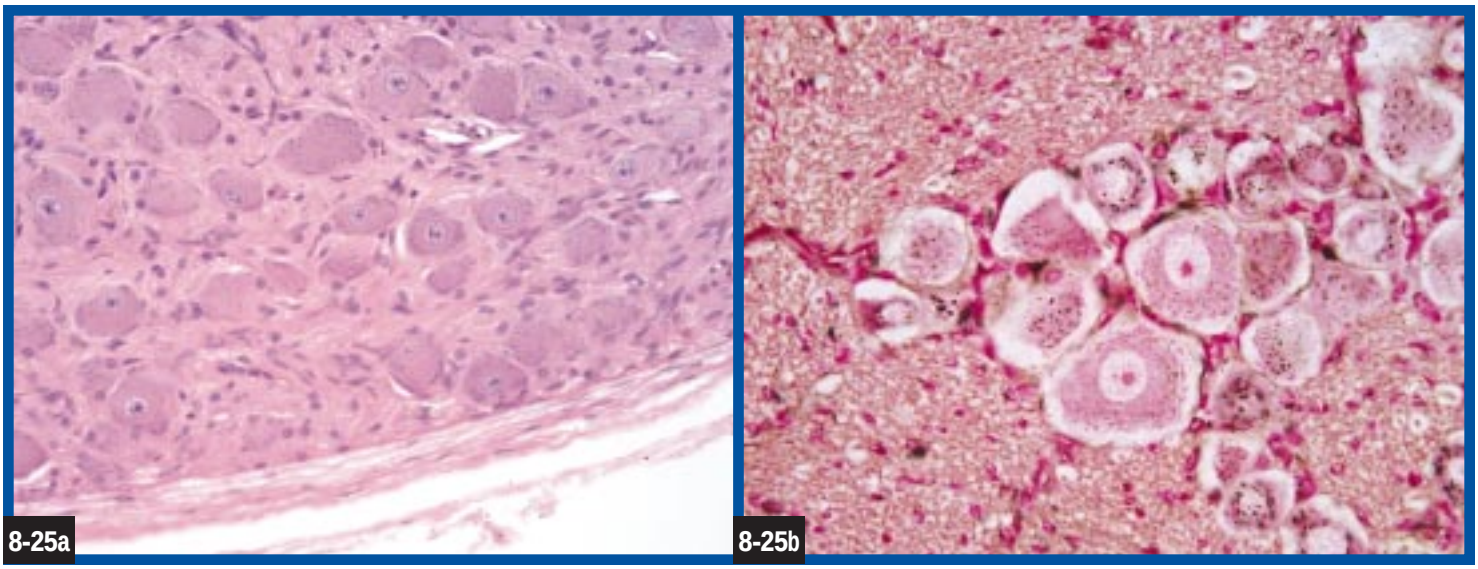
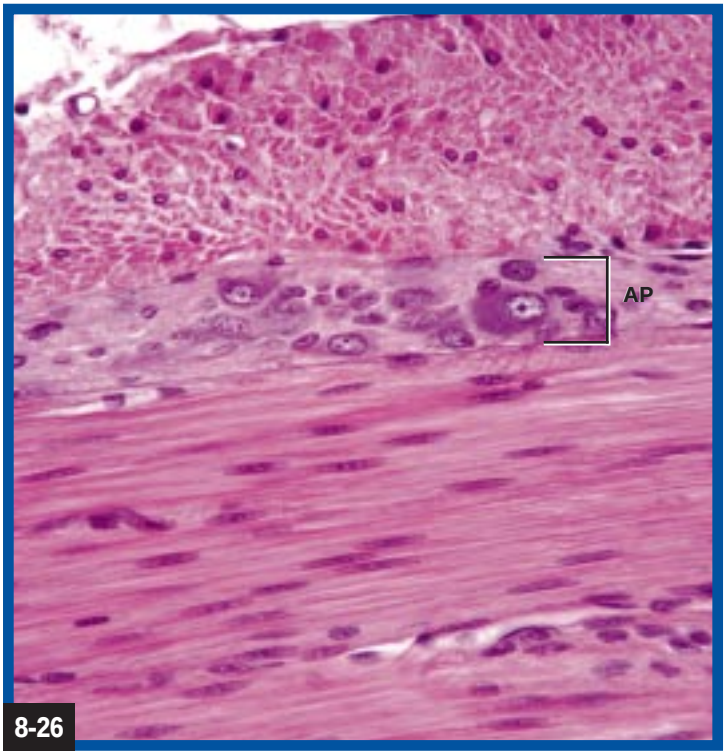
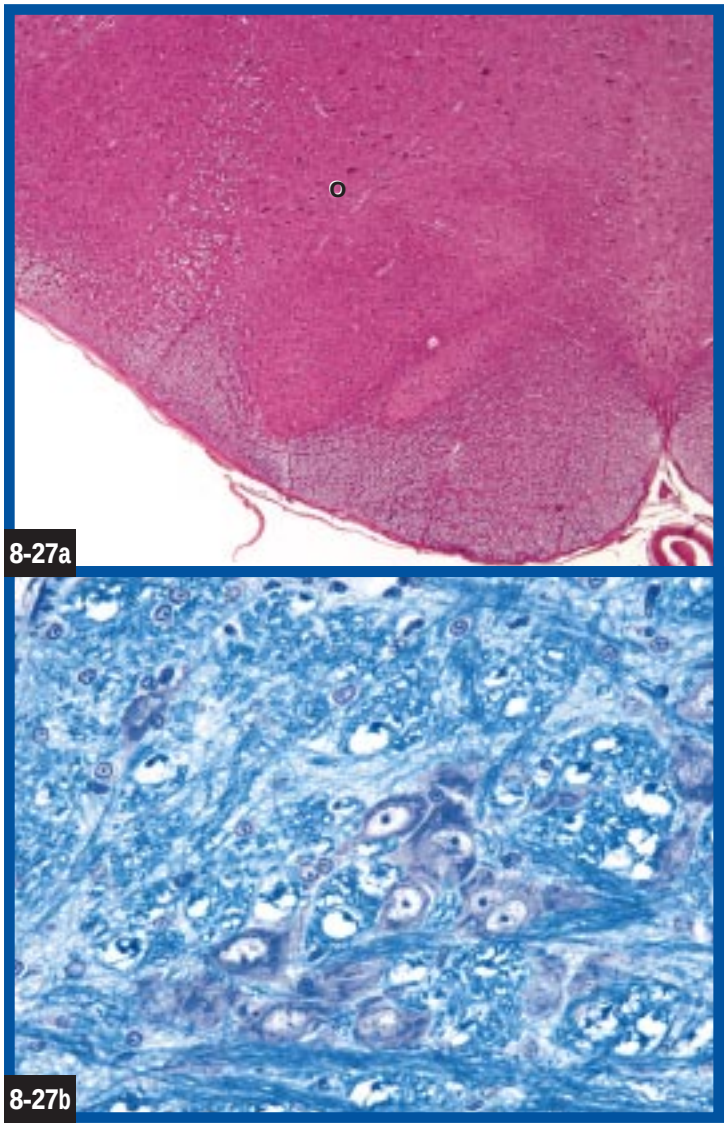


AUTONOMIC GANGLIA (a) Sympathetic postganglionic neuron cell bodies are seen in this sympathetic ganglion. The neurons are multipolar and satellite cells, while present, are fewer in number than in dorsal root ganglia. Also note the connective tissue between neurons. (*X230*) (b) In addition to the features visible in (a), the neurons in this ganglion show brown lipofuchsin granules, which are thought to be breakdown products from lysosome activity. They increase in number with age. *(X320)*



AUERBACH'S PLEXUS Some ganglia are embedded in other organs. Neurons serving the musculature of the digestive tract are located between muscle layers in the digestive organs and form Auerbach's plexus (AP). The submucosal plexus (Meissner's plexus) is responsible for regulating glandular activity. *(X380)*



NUCLEI IN THE CNS Groups of functionally related neuron cell bodies in the CNS are called nuclei. The olivary nucleus (O) of the medulla oblongata is seen in (a). (*X20*) (b) Part of a nucleus in the brain is shown in this micrograph. *(X320)*

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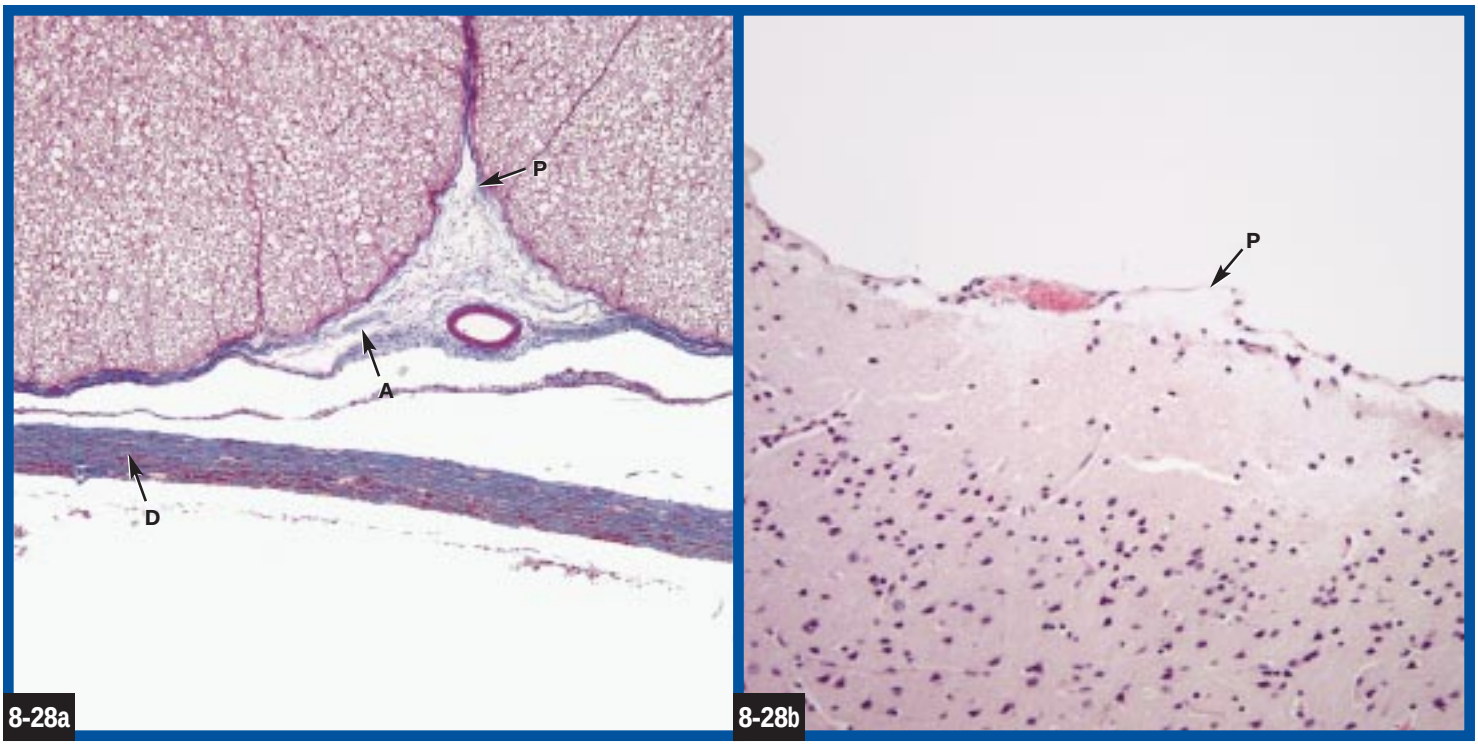
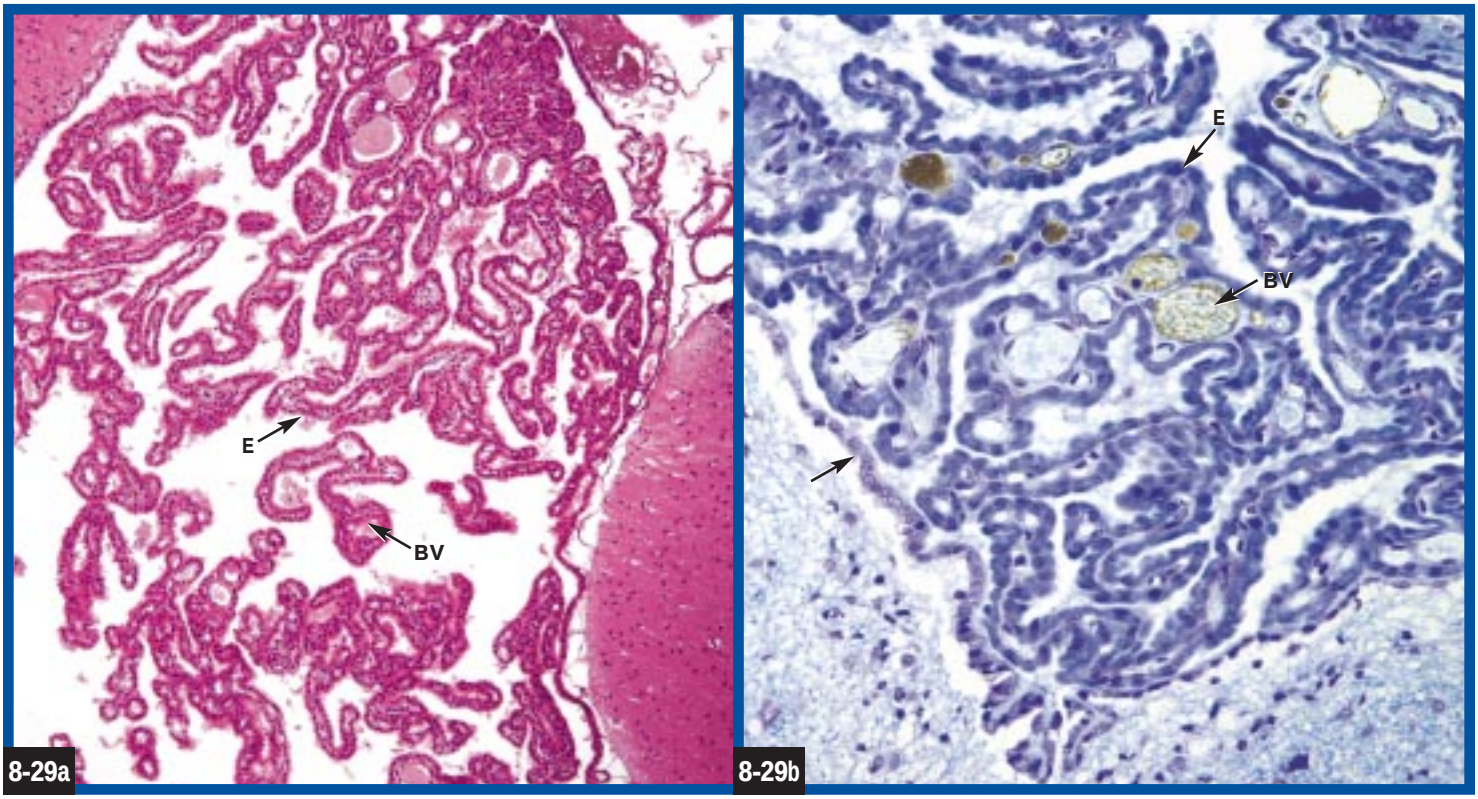


MENINGES (a)The three meningeal layers are visible in this spinal cord specimen. The outermost dura mater (D) has pulled away from the arachnoid (A) during preparation. The pia mater (P) is visible as a blue line on the surface of the cord. (*X65*) (b) A blood vessel is visible in the pia mater (P) of this cerebrum specimen. The other meningeal layers have been removed. *(X130)*



CHOROID PLEXUS The vascular choroid plexus is formed from pia mater and ependymal cells. (a) This micrograph shows choroid plexus from the fourth ventricle. Ependymal cells (E) and blood vessels (BV) are visible. The cerebellum is in the lower right corner of the image. (*X65*) (b) This specimen was magnified X250 and shows more detail than (a). Ependymal cells lining the ventricle are also visible, though some have pulled away from the neural tissue during preparation (arrow).

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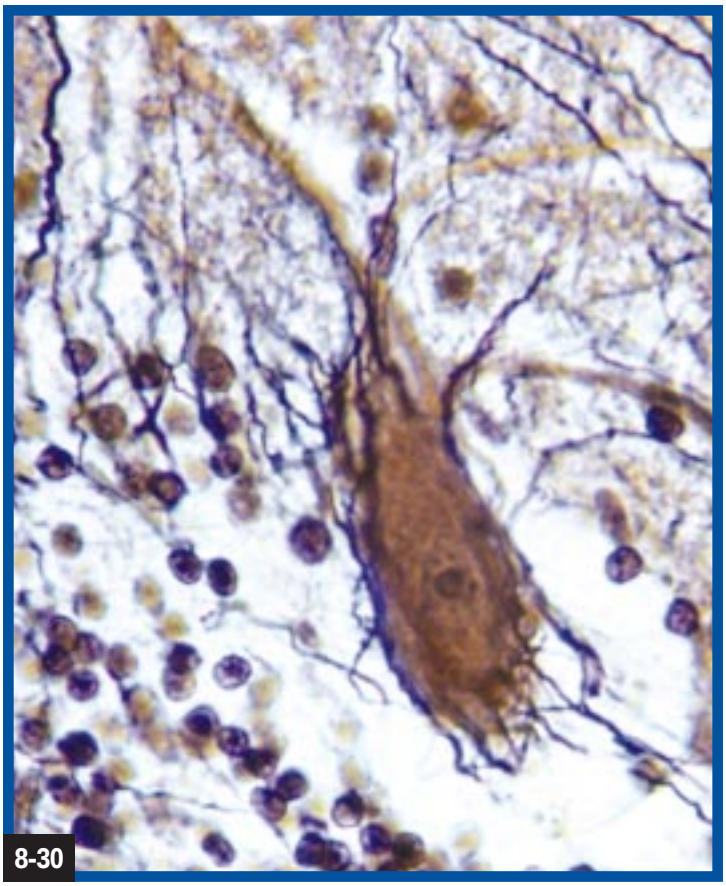
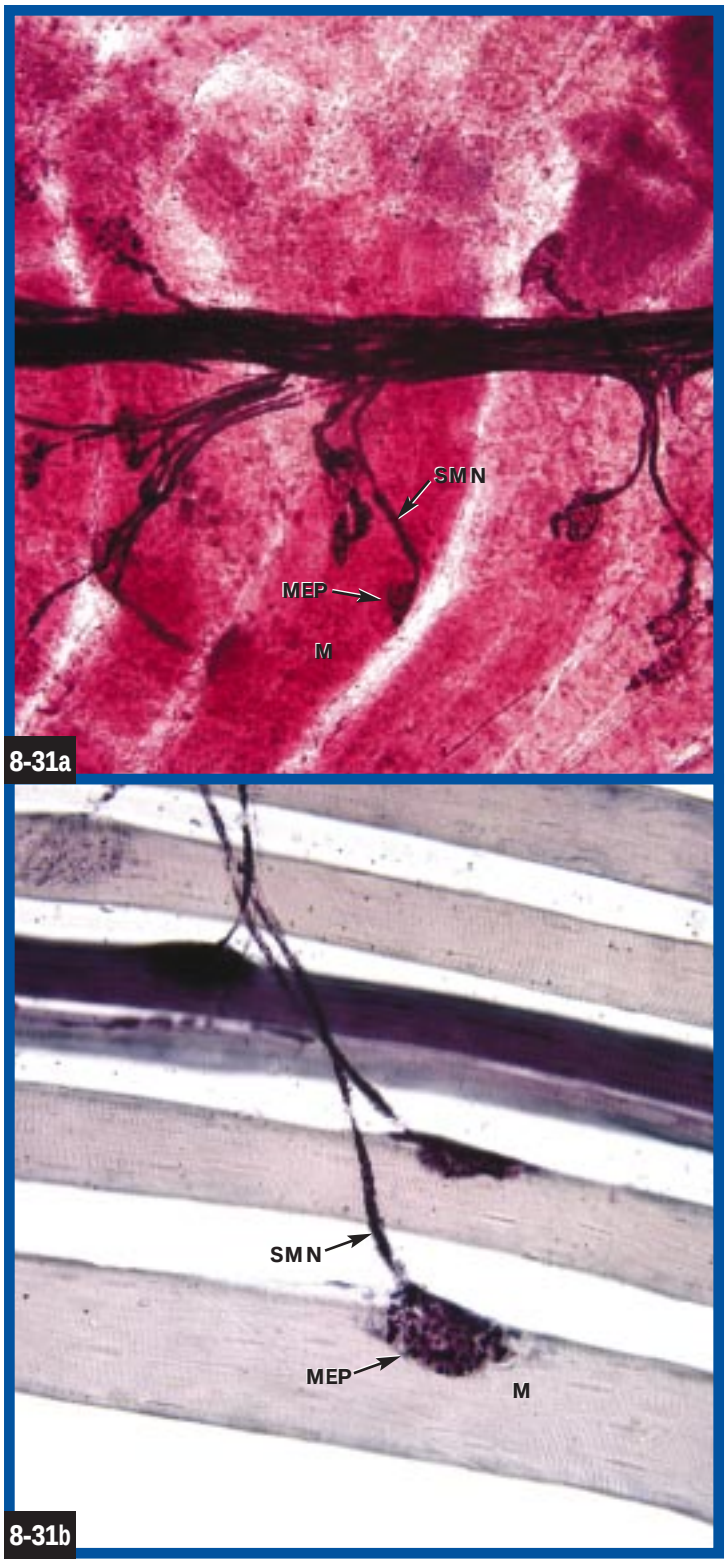


SYNAPSES The synapses between several axons and the cell body (axosomatic) and dendrites (axodendritic) of a Purkinje cell in the cerebellum are shown in this micrograph. *(X380)*



MOTOR END PLATES Motor end plates (MEP) contain the synapse between a somatic motor neuron (SMN) and a skeletal muscle fiber (M). They are complex structures made from the membranes of both cells. (a and b X250)

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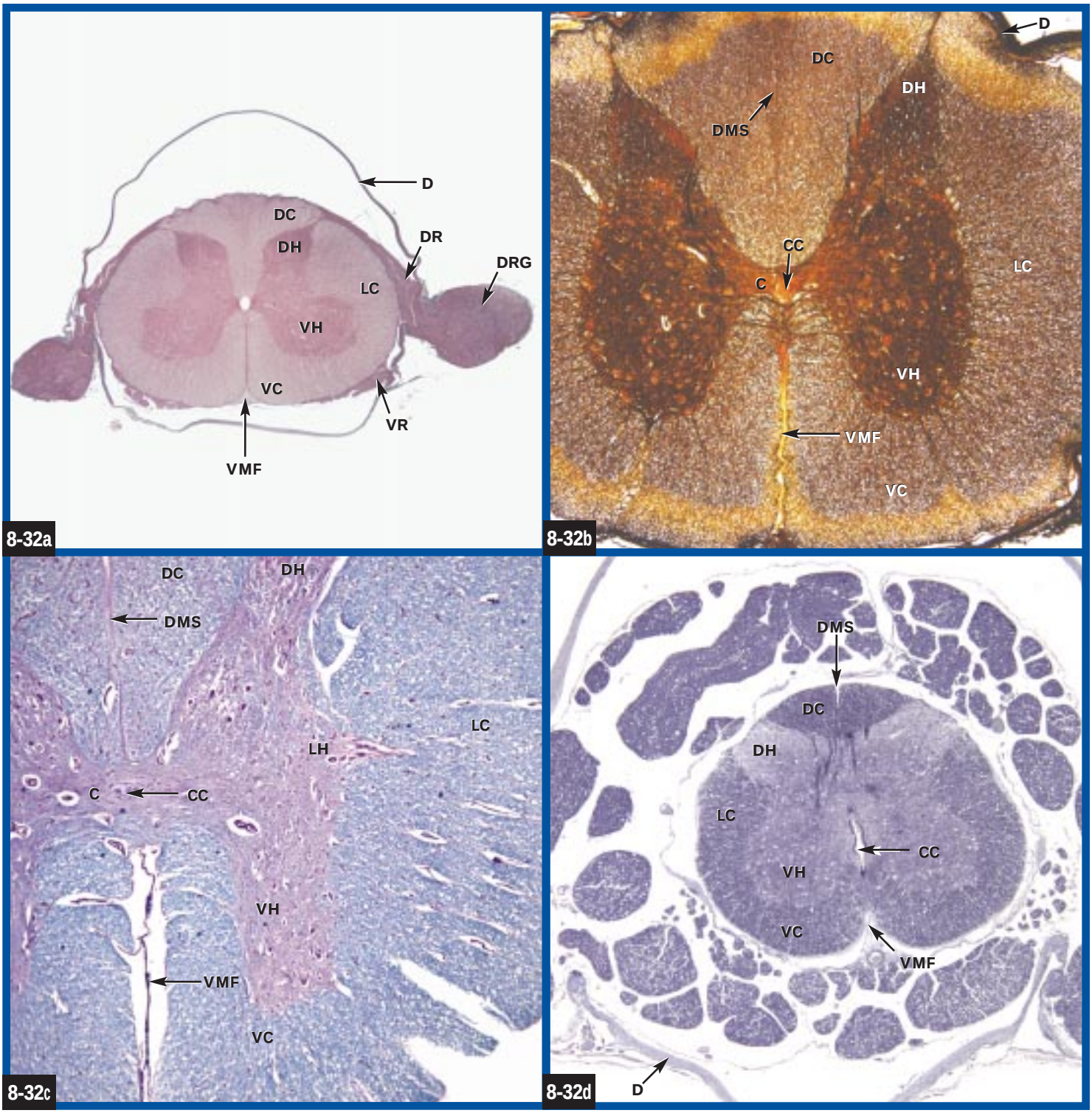

SPINAL CORD IN CROSS SECTION These four micrographs are of spinal cords from different specimens and regions. Specimens (a) and (c) are from the thoracic region. Specimens (b) and (d) are from the cervical and lumbar regions, respectively. All were magnified X25. Key to symbols used: **DH** = dorsal gray horn, **VH** = ventral gray horn, **LH** = lateral gray horn, **DC** = dorsal white column, **LC** = lateral white column, **VC** = ventral white column, **C** = central commissure, **CC** = central canal, **DRG** = dorsal root ganglion, **DR** = dorsal root, **VR** = ventral root, **D** = dura mater, **VMF** = ventral median fissure, and **DMS** = dorsal median sulcus.

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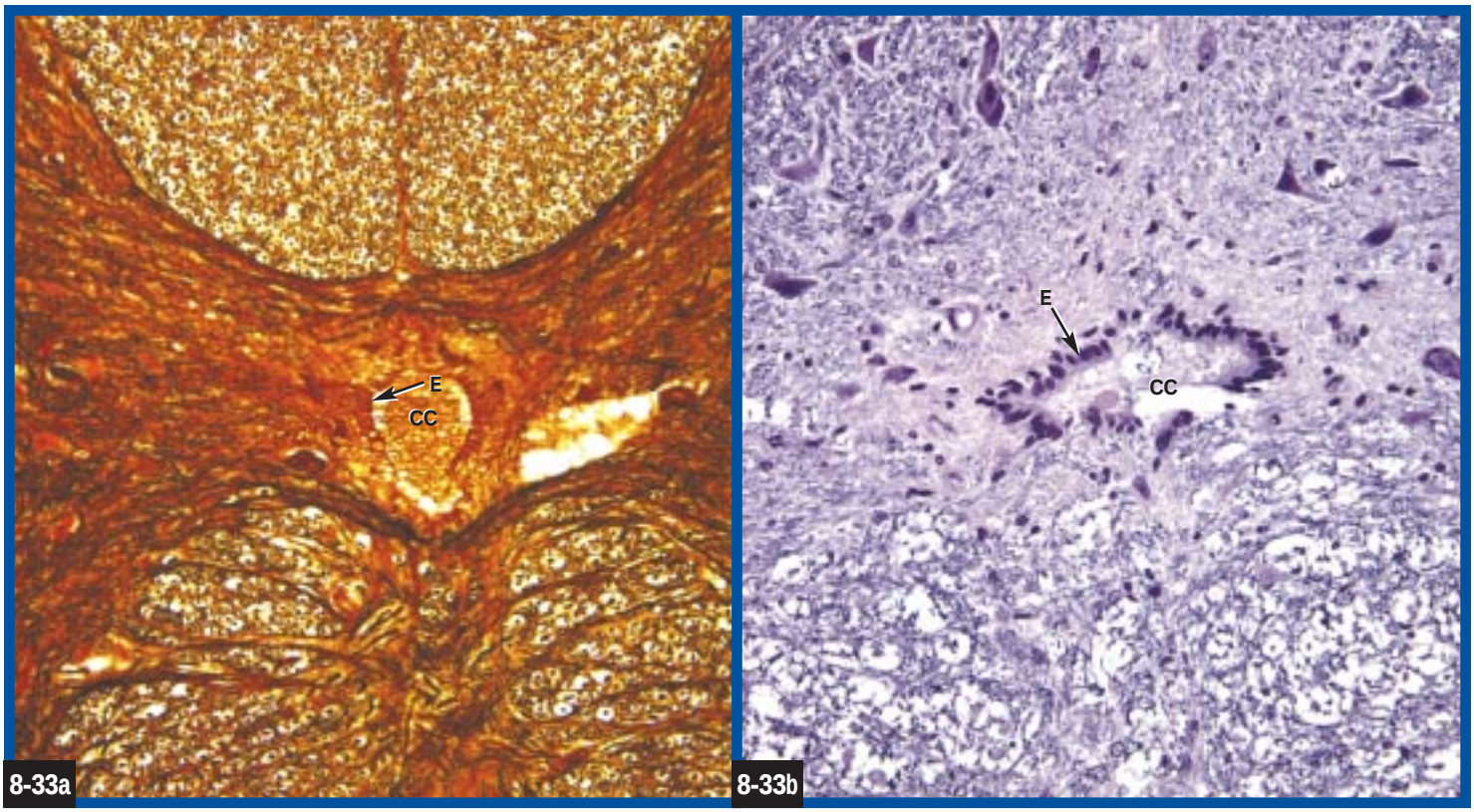
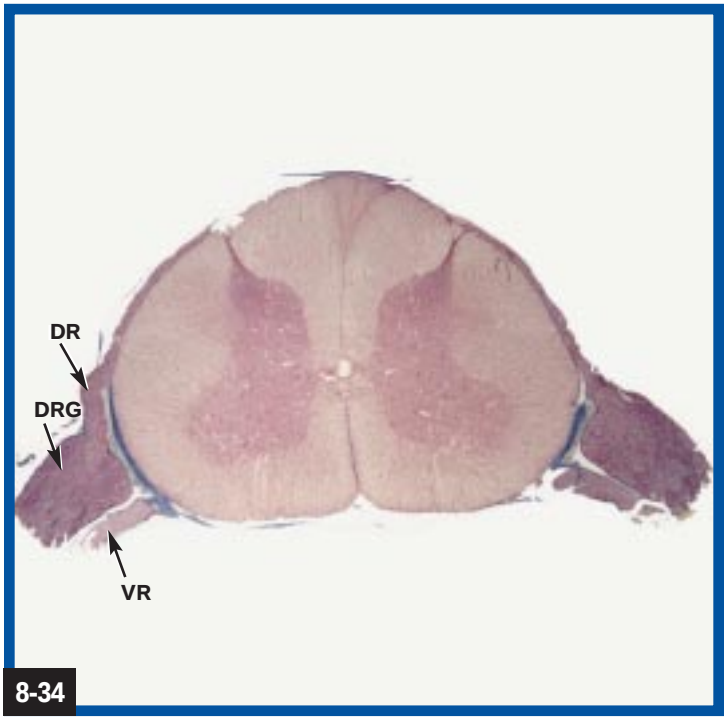
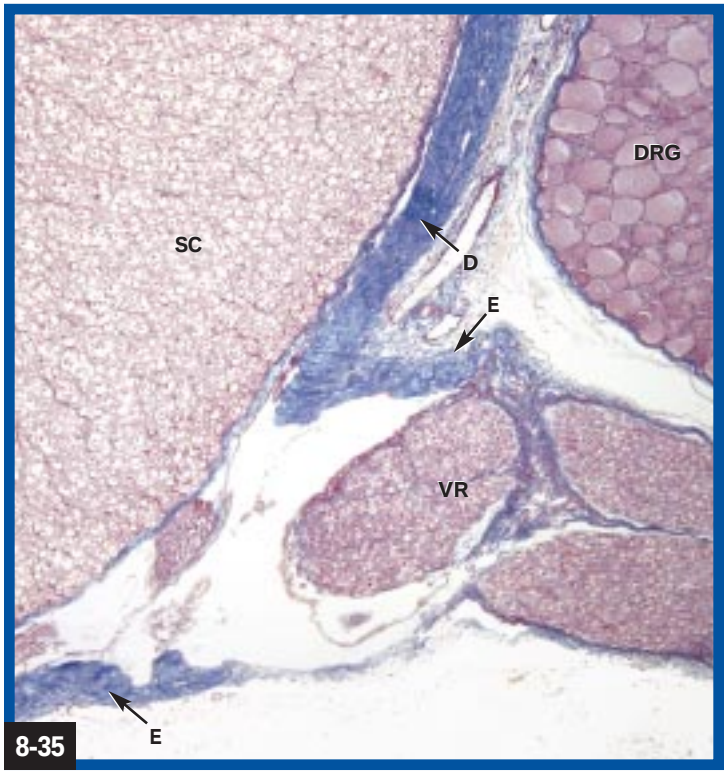


CENTRAL COMMISSURE AND CENTRAL CANAL OF SPINAL CORD (a) The central commissure is gray matter, but also contains fibers crossing from one side of the cord to the other. The central canal (CC) is lined with ependymal cells (E) and contains cerebrospinal fluid. (*X130*) (b) The central canal. *(X250)*



SPINAL NERVE ROOTS Each spinal nerve is attached to its segment of the spinal cord by two roots. The dorsal root (DR) carries sensory fibers entering the cord. The cell bodies of these sensory neurons are located in the dorsal root ganglion (DRG). The ventral root (VR) carries motor fibers out of the cord. *(X6)*



DURA MATER AND EPINEURIUM The dura mater (D) and epineurium (E) form a continuous layer where the nerve roots join the spinal cord. The ventral root (VR), and dorsal root ganglion (DRG), and spinal cord (SC) are shown. *(X65)*

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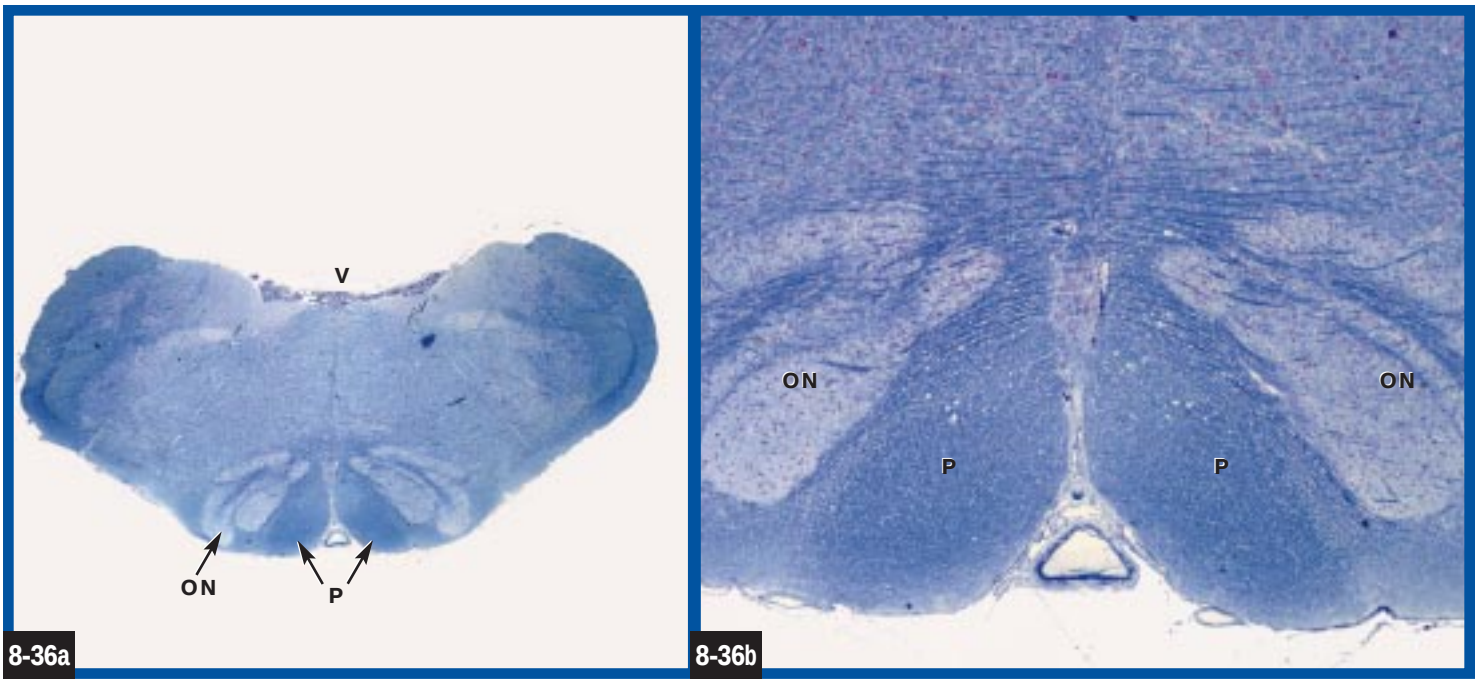
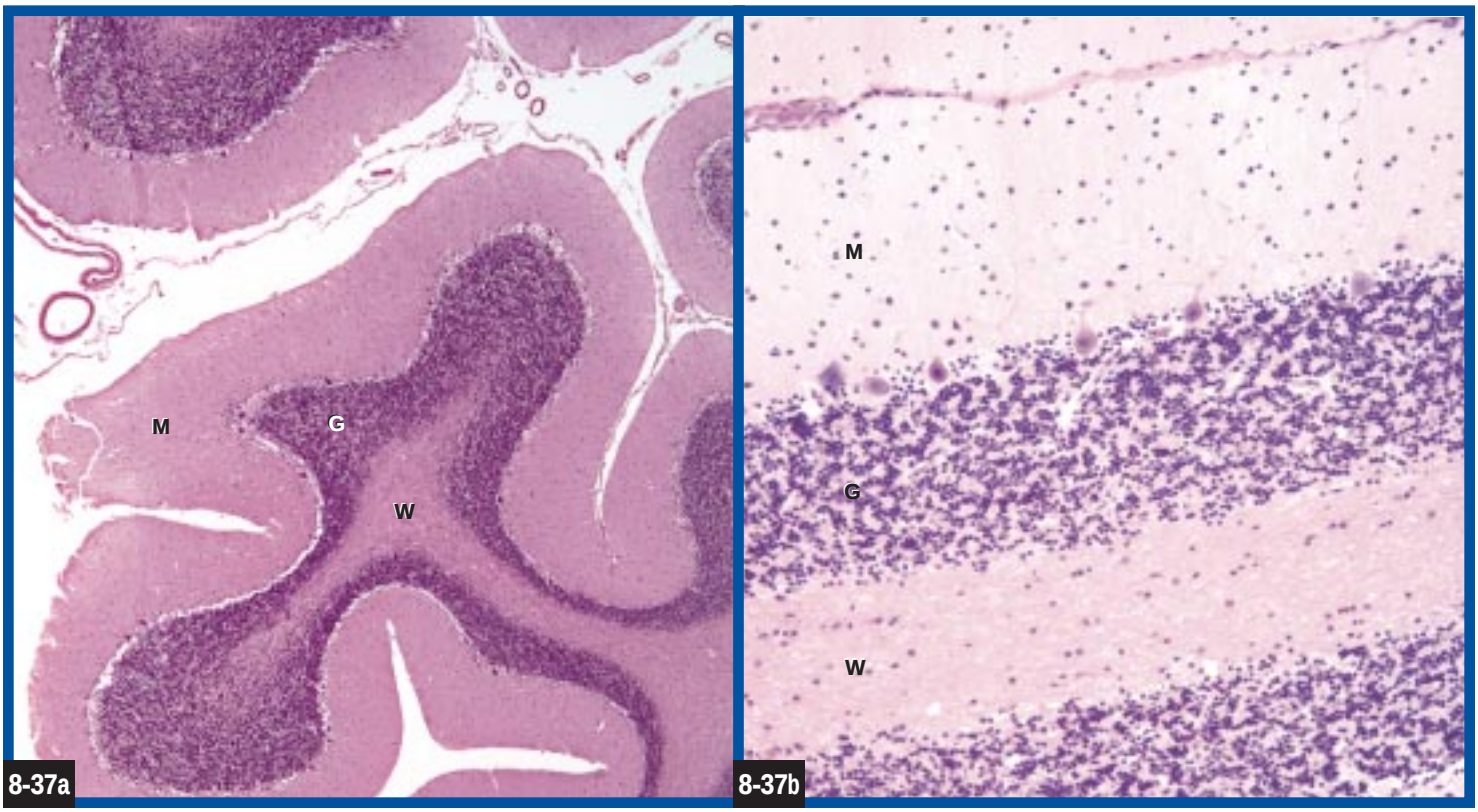


MEDULLA OBLONGATA The medulla oblongata houses ascending and descending tracts, and several nuclei. (a) This is a panoramic view of the medulla magnified X6. The fourth ventricle (V) is at the top. At the bottom are the pyramids (P), which are major descending tracts. The olivary nucleus (ON) is also visible. (b) This is a higher magnification of the olivary nuclei and the pyramids. *(X25)*



CEREBELLUM The cerebellum is involved in coordinating motor functions. Its surface is convoluted and it consists of gray matter around white matter. The gray matter is the cerebellar cortex and is divided into a superficial molecular layer (M) and a deeper granular layer (G). The white matter (W) carries fibers entering and leaving the cerebellum. (*X25*) (b) This micrograph was magnified X130 and shows the layers in the cerebellum.

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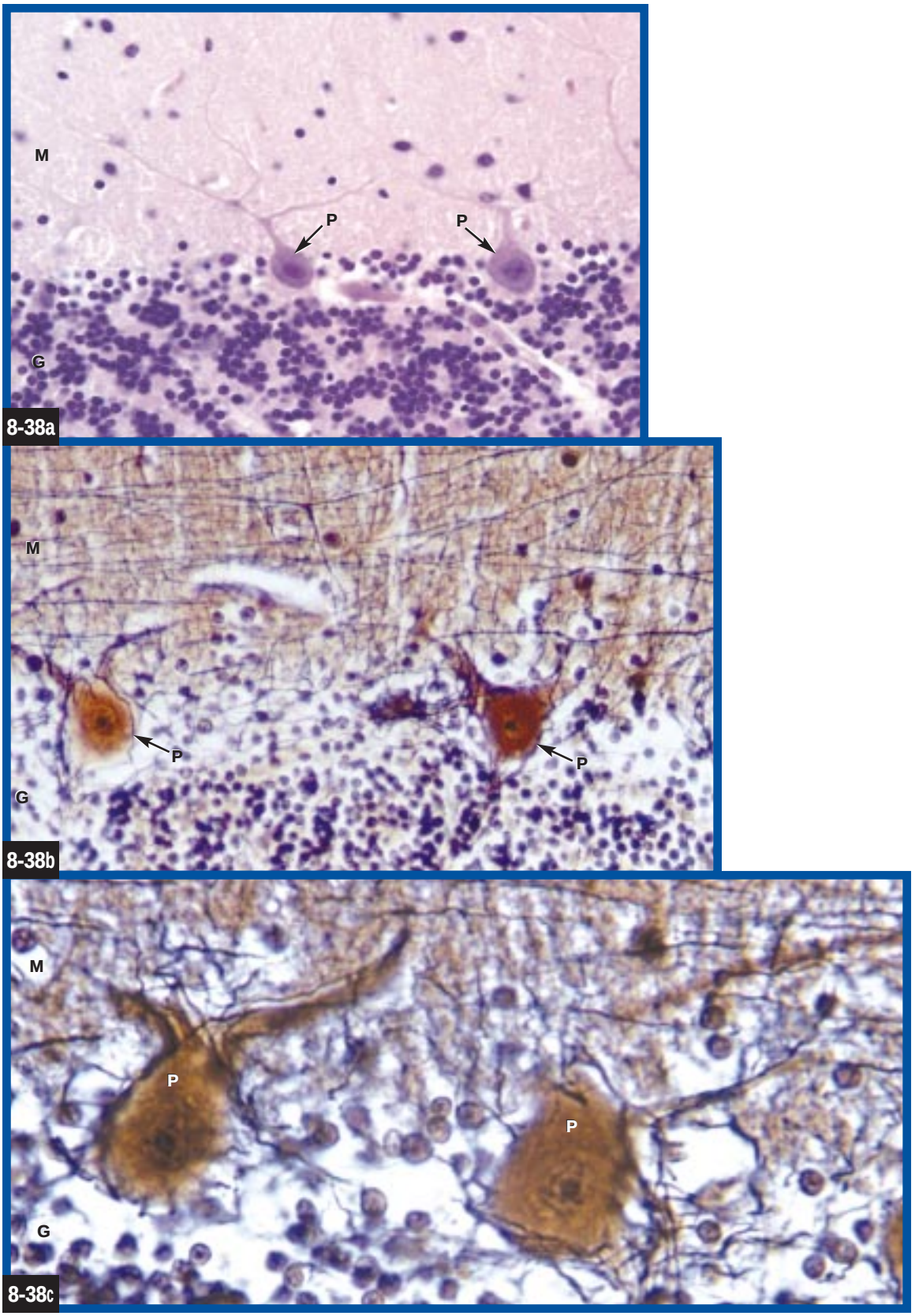

PURKINJE CELLS The most distinctive cells of the cerebellum are the Purkinje cells (P). They are found at the junction of the molecular (M) and granular (G) layers. They have highly branched dendrites that enter the molecular layer. Their single axon penetrates the granular layer. (a) This micrograph illustrates the branched dendrites of Purkinje cells. (*X320*) (b) The fibers in the molecular layer are visible in this specimen stained with a silver stain. (*X320*) (c) Axosomatic and axodendritic synapses on the Purkinje cells are visible in this micrograph. *(X425)*

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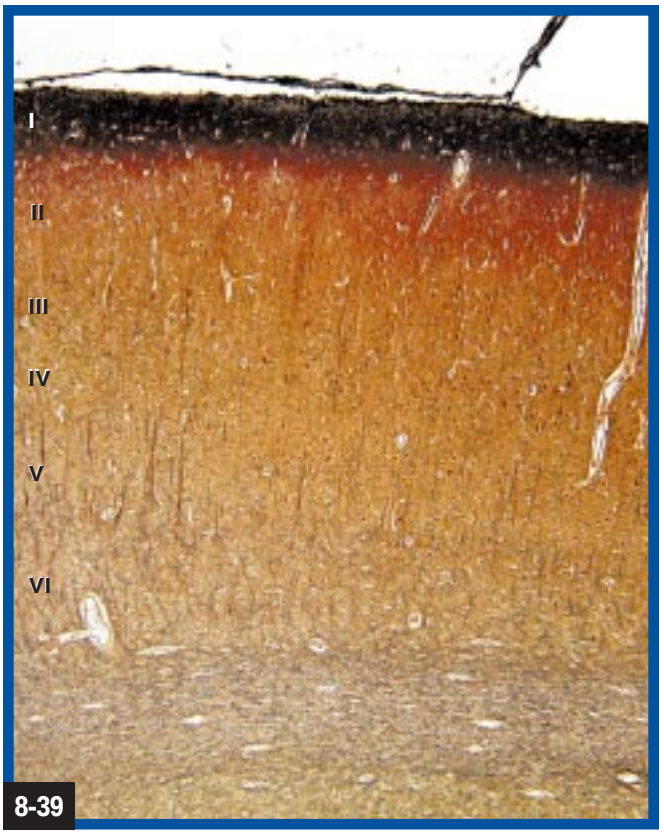
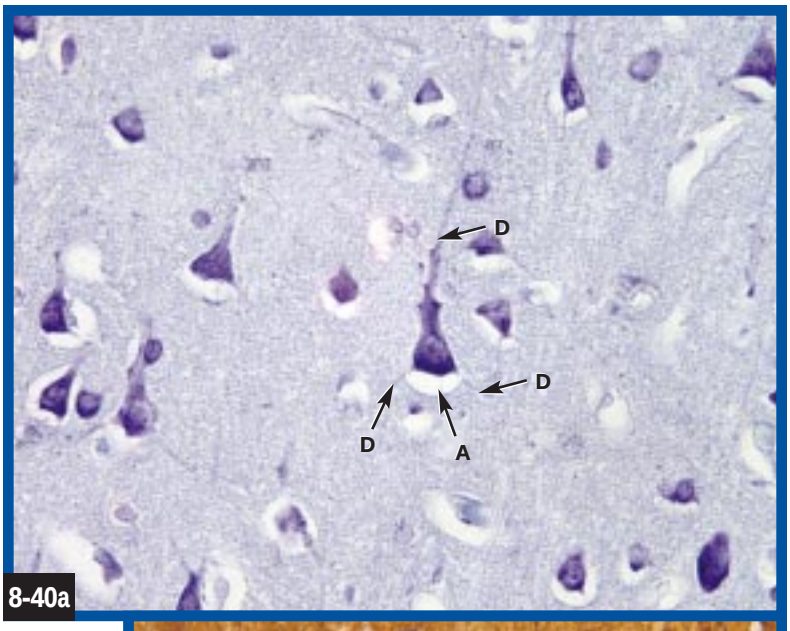
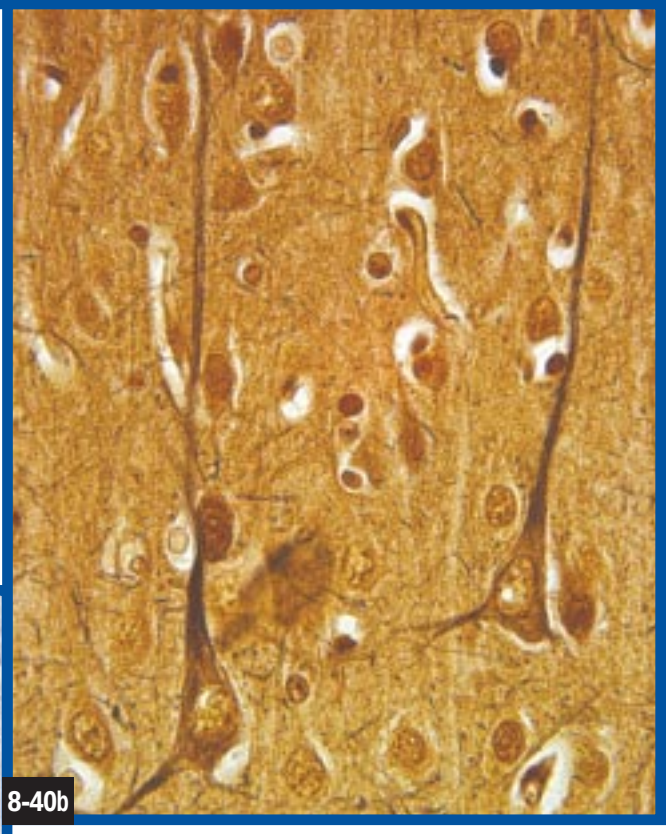
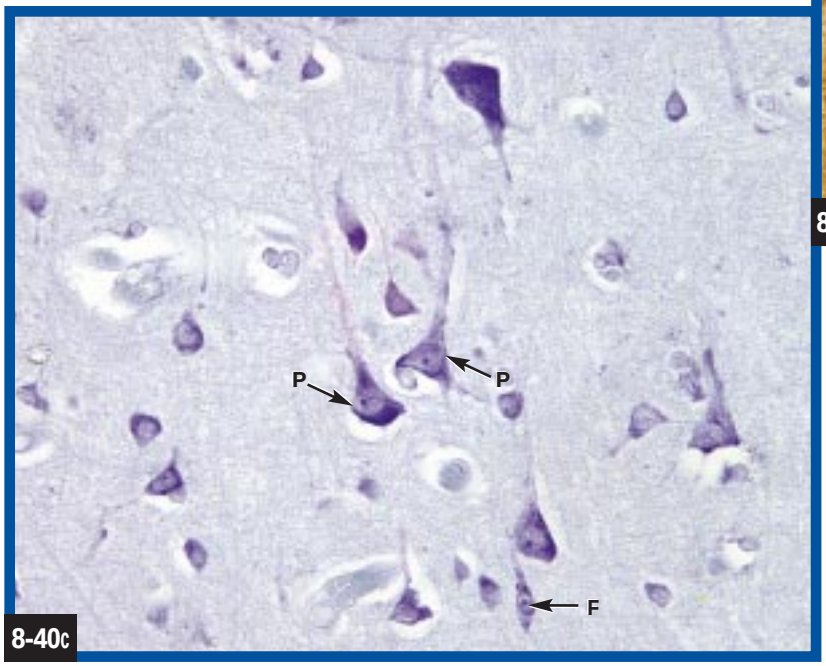


Cerebral Cortex The cerebral cortex is a thin layer of gray matter. In most parts of the cerebrum, it is divided into six layers. From superficial to deep: (I) Molecular layer, (II) Outer granular layer, (III) Pyramidal cell layer, (IV) Inner granular layer, (V) Ganglionic layer, (VI) Multiform cell layer. *(X50)*







Cells of the Cerebral Cortex (a) The most distinctive cells of the cortex are the pyramidal cells. Their apex is pointed toward the surface. The axon (A) emerges from the other end. Dendrites (D) are found at the apex and at the corners of the base. Pyramidal cells are found in Layers III and V, with the larger ones being deeper in the cortex. (*X320*) (b) Two pyramidal cells are seen in this specimen stained with a silver stain. (*X530*) (c) Fusiform cells (F) have a single axon emerging from the side and dendrites coming off both ends. Pyramidal cells (P) are also seen in this specimen. *(X320)*

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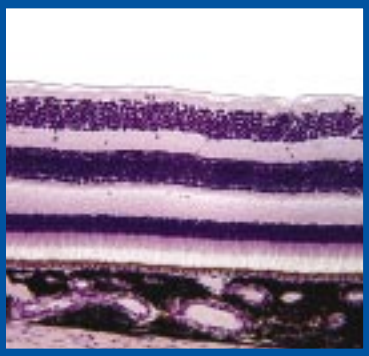
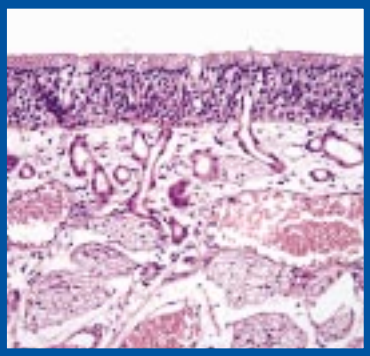
Special Sensory Organs

CHAPTER 9





Introduction to the Senses

Sensory receptors receive and respond to stimuli arising either from within the body or from the external environment. They are divided into receptors of the **general senses** and the **special senses**.

General sensory receptors are simple in construction and are widely distributed in the body. Examples include touch receptors **(Meissner's corpuscles)** and pressure receptors **(Pacinian corpuscles)** of the skin, which are covered in Chapter 11. Other general sensory receptors are covered in their respective chapters.

The special senses include taste, smell, vision, hearing, and balance and equilibrium. Their receptors are more complex in construction and are more localized. They are the topic of this chapter.

Olfactory Receptors

The receptors for olfaction are the simplest of the special senses. Olfactory epithelium covers the upper nasal cavity and superior nasal conchae (Figure 9-1). It is a modified PSCC that contains the **olfactory receptor cells**, which are bipolar neurons. The end of the dendrite is dilated to form an **olfactory vesicle**, whereas its axon passes through a foramen of the cribriform plate to synapse with second order neurons in the **olfactory bulb**.

Two other cells are located in the olfactory epithelium. **Basal cells** are small and located near the basement membrane. They are a source of new cells. Tall **supporting (sustentacular) cells** provide physical and nutritive support to the receptor cells. The three cell types are difficult to differentiate in H&E stained specimens, but nucleus location provides a high percentage basis for identification. The nuclei of basal cells are located in lower third of the epithelium, while nuclei of sustentacular cells are near the surface. The nuclei of olfactory receptor cells are in the middle.

The connective tissue deep to olfactory epithelium (lamina propria) contains **Bowman's glands**. These serous glands produce a watery secretion that dissolves odoriferous chemicals and makes them more able to stimulate the receptors.

Taste Buds

Taste buds (Figure 9-2) are found in the epithelium of the tongue as well as other parts of the oral mucosa and house the chemoreceptors for the sensation of taste. They are oval-shaped with an opening at the surface called the **taste pore**. Internally, lighter staining **gustatory cells** and darker **sustentacular cells** have long microvilli that project into the taste pore. While both cells are associated with neurons, the gustatory cells are considered to be the actual chemoreceptors. Electron micrographs have revealed **basal cells**, a third cell type that may be the source of new cells.

The Eye

The eyeball is the site of photoreceptors responsible for vision. It is composed of three basic layers (Figure 9-3). From external to internal, they are the **fibrous tunic (tunica fibrosa)**, the **vascular tunic (tunica vasculosa)**, and the **neural tunic (tunica nervosa)**. In addition, there are two cavities in the eye. The **anterior cavity** is anterior to the lens and contains

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the watery **aqueous humor**. The **posterior cavity** is posterior to the lens and occupies the greatest volume of the eye. It contains the gel-like, refractive **vitreous body**.

Fibrous Tunic

The fibrous tunic is mostly composed of the **sclera**, with the anterior one-sixth forming the **cornea**. The sclera is made of densely arranged collagen fibers, which accounts for its white appearance. It is an attachment site for the ocular muscles and is continuous with the dura mater of the optic nerve.

The cornea (Figure 9-4) is transparent and avascular with five distinct layers. On the anterior, the **corneal epithelium** is a thin, nonkeratinized stratified squamous epithelium that is continuous with the **conjunctival lining** of the inner eyelid. It has numerous nerve endings in it. Deep to the corneal epithelium is **Bowman's membrane**, a thin basal lamina made of collagen. The **stroma** is the thickest layer and is composed of up to 250 lamellae of collagen fibers. The fibers in each lamella are parallel, but the fibers in adjacent lamellae are oriented in different directions. The **canal of Schlemm** is found in the stroma at the **sclero-corneal junction** (Figure 9-5). **Descemet's membrane** is a thick basement membrane between the stroma and the corneal endothelium. The posterior of the cornea is lined with a simple squamous **corneal endothelium**. Among other functions, the corneal endothelium keeps the stroma dehydrated to maintain optical qualities.

Vascular Tunic

Deep to the fibrous tunic is the vascular tunic. It is composed of the choroid, ciliary body, and iris. The **choroid** (Figure 9-6) is made of loose connective tissue. It is highly vascular and contains an abundance of **melanin**, a black pigment.

The **ciliary body** (Figure 9-7) is a circular expansion of the vascular tunic even with the lens. **Ciliary processes** (Figure 9-8) extend from the ciliary body and produce **aqueous humor**, which occupies the anterior cavity of the eye (see below). **Suspensory ligaments of the lens** also extend from the ciliary processes and insert on the lens. Smooth **ciliary muscle** within the ciliary body adjusts tension on the suspensory ligaments and in turn on the lens, thus changing its shape and allowing it to focus light on the retina.

The **iris** (Figure 9-9) is the colored part of the eye. It separates the **anterior chamber** and the **posterior chamber** of the anterior cavity. The hole in its center is the **pupil**. On the posterior surface of the iris is a layer of **melanocytes**. The more abundant they are, the darker the eyes. Internally, there are smooth muscles arranged circularly and radially around the pupil. The former is the **sphincter pupillae muscle** and is responsible for constriction of the pupil in conditions of high light intensity. The latter is the **dilator pupillae muscle**, which is responsible for its dilation when it is darker.

Aqueous humor is derived from capillaries in the ciliary processes. It flows from the posterior chamber, through the pupil, into the anterior chamber, and is returned to the blood by the canal of Schlemm. Aqueous humor supplies the lens and cornea with oxygen and nutrients.

The lens (Figure 9-10) is a biconvex transparent disc. Its flexibility allows it to change shape (as a result of changes in tension brought about by contraction and relaxation of the ciliary muscle) and bring images into focus on the retina. It consists of three layers. On the surface is a transparent, collagenous **lens capsule**. The second layer is a simple cuboidal **subcapsular epithelium** that lies deep to the capsule on the anterior surface. Finally, up to 3000 elongated and hexagonal **lens fibers** make up the greatest portion of the lens. As they mature, they elongate along the antero-posterior axis of the lens and lose their organelles. The fibers' refractive ability derives from the accumulated protein **crystallin** contained in them.

Neural Tunic

The photoreceptor cells of the **retina** are called **rods** and **cones**. Their complex shape includes a **nuclear region** (cell body), which contains the nucleus. Extending posteriorly from the nuclear region are **inner** and **outer segments**. The shape of the outer segment, which contains pigments, is the basis for naming rods and cones. Extending anteriorly from the nuclear region is a **synaptic region**.

Functionally, rods and cones differ in the amount of light necessary to stimulate them. Rods are stimulated in low light intensity and are responsible for monochromatic ("black and white") vision. Cones are only stimulated by higher light intensities and are responsible for color vision.

The **retina** (Figure 9-11) consists of ten layers. With their complex shapes and their orientation perpendicular to the retina, different parts of rods and cones show up in several of the layers. The layers are listed below from outside to inside.

- A **pigmented epithelium** abuts the choroid. It is composed of short columnar cells that accumulate melanin. This pigment absorbs light that has not been absorbed by the rods and cones and prevents reflection back into the eye. The pigment cells also surround the rod and cone segments.
- The **photoreceptive layer** contains the rod and cone segments.
- The thin acidophilic e**xternal limiting membrane** is not a membrane at all. It is a region of tight junctions between **Muller cells** (large glial cells—see the next page) and the rods and cones.
- The **outer nuclear layer** consists of densely packed rod and cone cell bodies and their nuclei.

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- The **outer plexiform layer** is a region of axodendritic synapses between the rods and cones and the next layer of (bipolar) neurons.
- The **inner nuclear layer** contains cell bodies of **bipolar neurons**, other neurons, and Muller cells.
- The **inner plexiform layer** is a region of axodendritic synapses between bipolar neurons and the neurons (ganglion cells) of the next layer.
- The **ganglion cell layer** contains cell bodies of **ganglion cells**, whose axons form the **optic tract**.
- The **optic nerve fiber layer** is composed of ganglion cell axons that converge at the optic disc and emerge as the **optic tract**. (Since the neural tunic is an outgrowth of the brain, the optic nerves are more appropriately referred to as "tracts.")
- The innermost retinal layer is the **inner limiting membrane**. It is the basal lamina of long glial cells called Muller cells that extend from the inner limiting membrane to the outer limiting membrane where they form tight junctions with the rods and cones. Muller cells physically and metabolically support rods and cones.

Where the optic tract emerges from the eye, there is no retina. This is the **blind spot** (Figure 9-12). A few millimeters lateral and slightly inferior to it is a small pit in the retina where visual acuity is greatest. This is the **fovea centralis**.

Eyelid and Conjunctiva

The **eyelid** (Figure 9-13) derives structural support from a plate of fibroelastic tissue called the **tarsus** and muscle fibers from the **orbicularis oculi** and **levator palpebrae** (in the upper eyelid) **muscles**. Anteriorly, it is covered with a thin skin. Posteriorly, it is covered by a stratified columnar epithelium with goblet cells that forms the **palpebral conjunctiva**. The palpebral conjunctiva reflects and covers the exposed portion of the sclera as the **bulbar conjunctiva**. The mucous secretions lubricate the eyelids and eye surface.

The Ear

The external ear consists of the **pinna (auricle)** and the **external auditory meatus**. The pinna (Figure 9-14) is composed of a framework of elastic cartilage covered with skin. It collects sound waves and funnels them through the external auditory meatus to the eardrum. The proximal part of the external auditory meatus is formed from elastic cartilage, while the distal portion is bone. Both are lined with skin containing glands that secrete **cerumen** (earwax). The fibrous **tympanic membrane** forms the partition between the external and middle ear.

Middle Ear

The **middle ear cavity** is a space within the temporal bone and is lined with simple cuboidal to simple squamous epithelium. It opens into the nasopharynx via the **auditory (Eustacian) tube**. The **ossicles** are three small bones (**malleus**, **incus**, and **stapes**) that link the tympanic membrane to the inner ear. Vibrations in the tympanic membrane due to sound waves are amplified by the ossicles.

Internal Ear

The internal ear is made of small cavities and channels hollowed out of the temporal bone. Collectively, these constitute the **osseous (bony) labyrinth**. The **membranous labyrinth** is contained within and conforms (more or less) in shape to the osseous labyrinth. Both are filled with fluid. The osseous labyrinth contains **perilymph**, whereas the membranous labyrinth contains **endolymph**. There are three regions in the internal ear—the vestibule, the semicircular canals, and the cochlea.

The **vestibule** (Figure 9-15) is the middle portion of the osseous labyrinth. Within it are the **utricle** and **saccule**. Both are made of membranous labyrinth. They are lined with a simple cuboidal epithelium and each contains a **macula** (Figure 9-16). The maculae are oriented at right angles to one another and are composed of receptor cells used in maintenance of balance and equilibrium. The actual receptors are **sensory hair cells** that have stereocilia and a single cilium **(kinocilium)** projecting into a gelatinous layer of glycoprotein. **Otoliths** made of calcium carbonate are also embedded in the glycoprotein. Head movements result in bending of the stereocilia and stimulation of the hair cells. The complex sensory input from hair cell stimulation is processed by the brain and used to determine the position of the head in space.

Extending posteriorly from the vestibule are three **semicircular canals** arranged at right angles to one another. **Semicircular ducts** made of membranous labyrinth are in each canal, both ends of which open into the utricle. The **ampulla** is a dilation at one end of each duct. It contains the **crista ampullaris** (Figure 9-17) which has **sensory hair cells** similar to those of the maculae. The **cupula** is a gelatinous glycoprotein layer that overlies each crista. Body movements result in inertia in the endolymph, which pushes on the cupulae and stimulates the hair cells. The complex pattern of hair cell stimulation is interpreted by the brain as movement in a particular direction at a particular rate.

The **cochlea** (Figure 9-15) contains the receptors for hearing. It consists of a spiral canal extending anteriorly from the vestibule. The bony labyrinth is divided into two separate canals by the membranous **scala media**, which is filled with endolymph. The scala **vestibuli** and **scala tympani** are on either side of the scala media and contain perilymph. Since the scala media does not extend the entire length of the cochlea, the scala vestibuli and scala tympani are continuous at the apex of the cochlea. The **modiolus** forms the bony axis of the cochlea.

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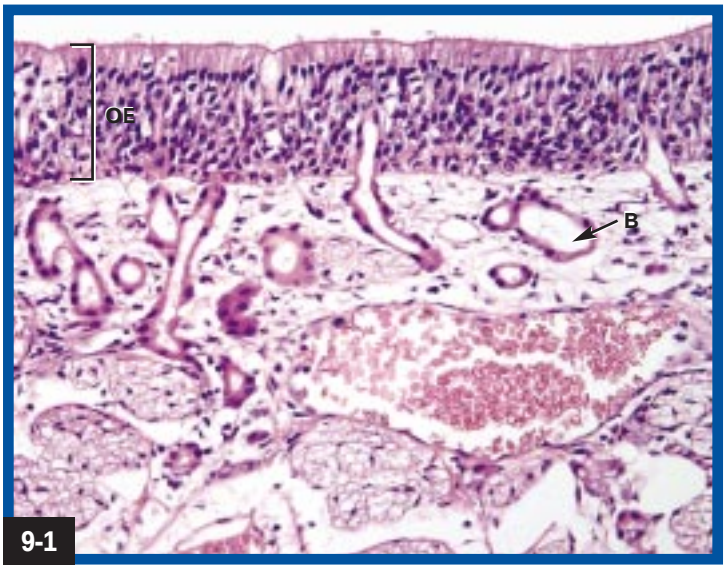
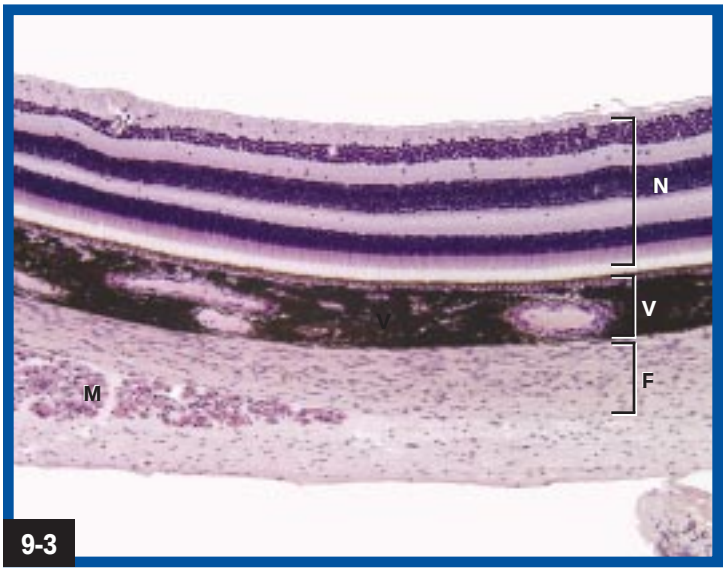
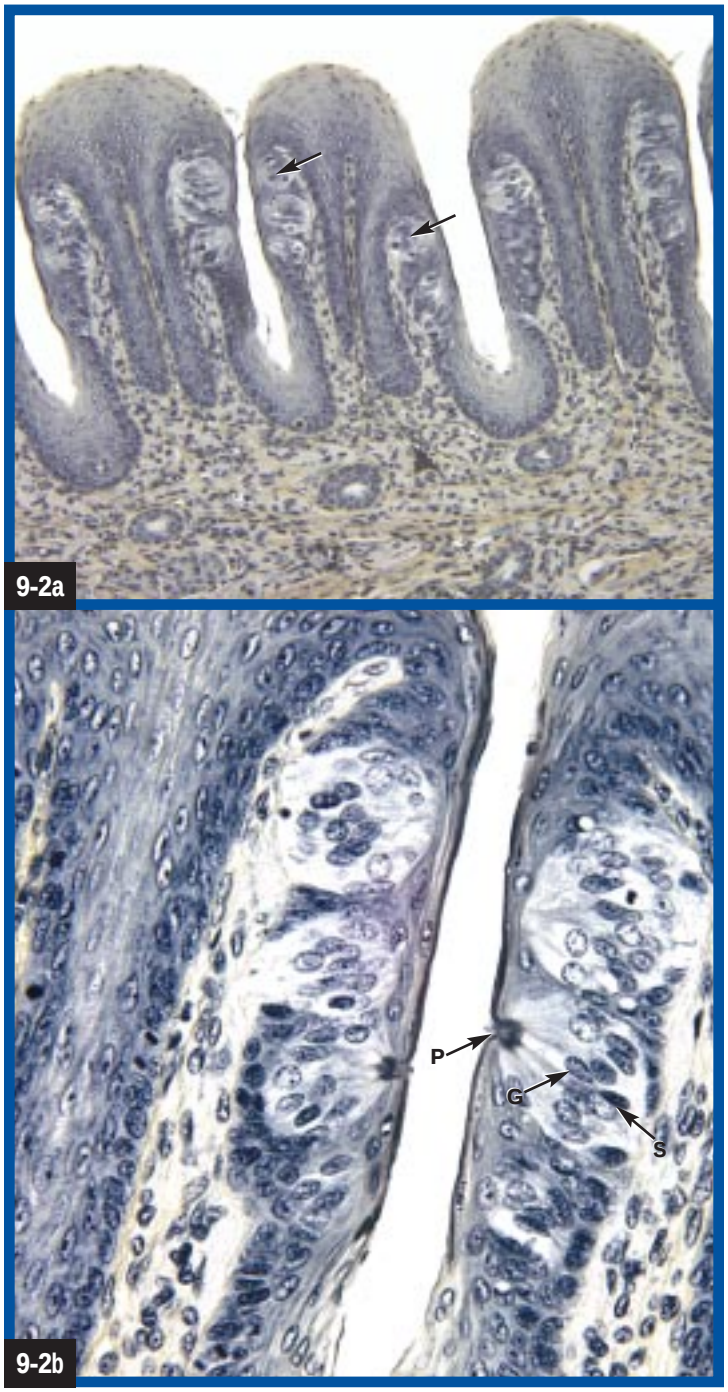
In cross section, the scala media looks triangular, with the **vestibular** and **basilar membranes** separating it from the scala vestibuli and scala tympani, respectively (Figure 9-18). Resting on the basilar membrane is the **organ of Corti** (Figure 9-19), which contains **hair cells** and **support cells**. The hair cells are the actual sound receptors and have stereocilia embedded in the **tectorial membrane** that overlies them. Vibration of a particular frequency (related to the wavelength of the sound that caused it) results in movement of a particular part of the basilar membrane. This stimulates the hair cells, which in turn stimulate the sensory bipolar neurons that occupy the **spiral ganglion** (Figure 9-20). Their axons form the auditory nerve. The auditory cortex interprets the information as sound of a particular pitch.



OLFACTORY EPITHELIUM Olfactory cells are the receptors for the sense of smell. They are located in the olfactory epithelium (OE), a modified PSCC in the nasal cavity. It is difficult to identify the three cell types of this epithelium in H&E stains, but nucleus location provides a means of making a good guess. Basal cells have nuclei in the lower third, nuclei of sustentacular cells are near the surface, and nuclei of olfactory cells are in the middle. Bowman's glands (B) and ducts are visible in the lamina propria. (*X210*)



LAYERS OF THE EYEBALL The three layers of the eyeball, from outside in, are the fibrous tunic (F), vascular tunic (V), and neural tunic (N). An ocular muscle (M) is also visible in this specimen. *(X50)*



TASTE BUDS Chemoreceptors for the sensation of taste are located in taste buds found in the epithelium lining the oral cavity. (a) Taste buds (arrows) on lingual papillae. *(X130)* (b) Detail of taste buds. Visible are the taste pores (P), gustatory cells (G) with light staining nuclei, and sustentacular cells (S) with darker nuclei. *(X380)*

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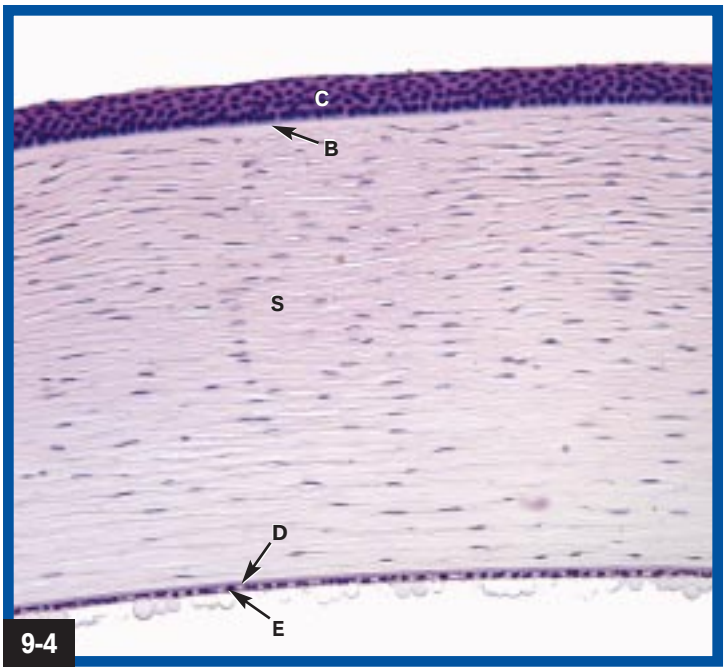
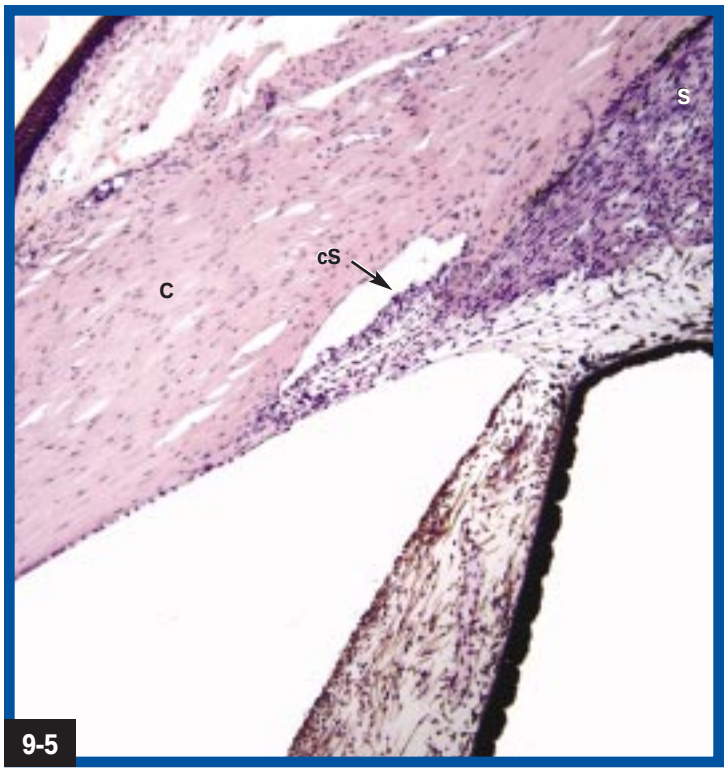
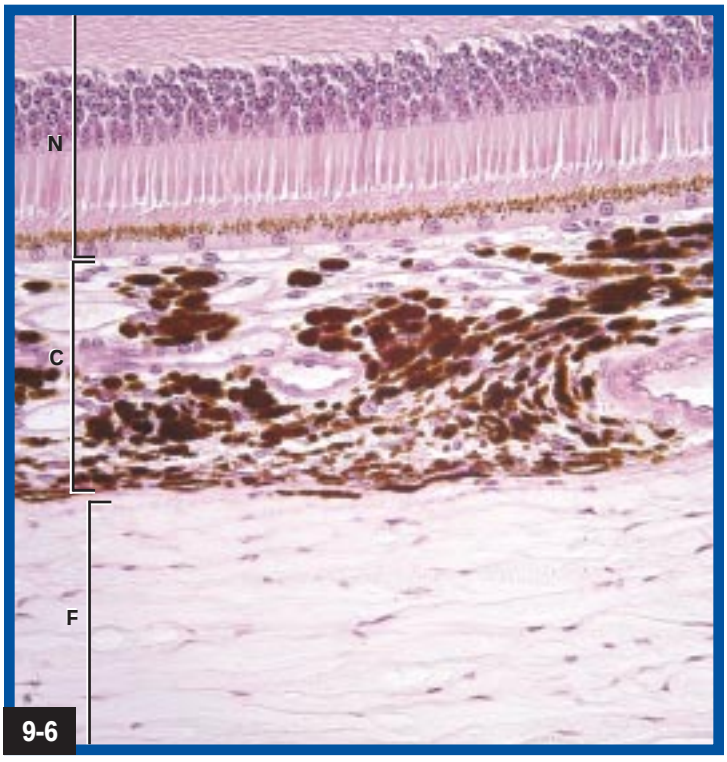


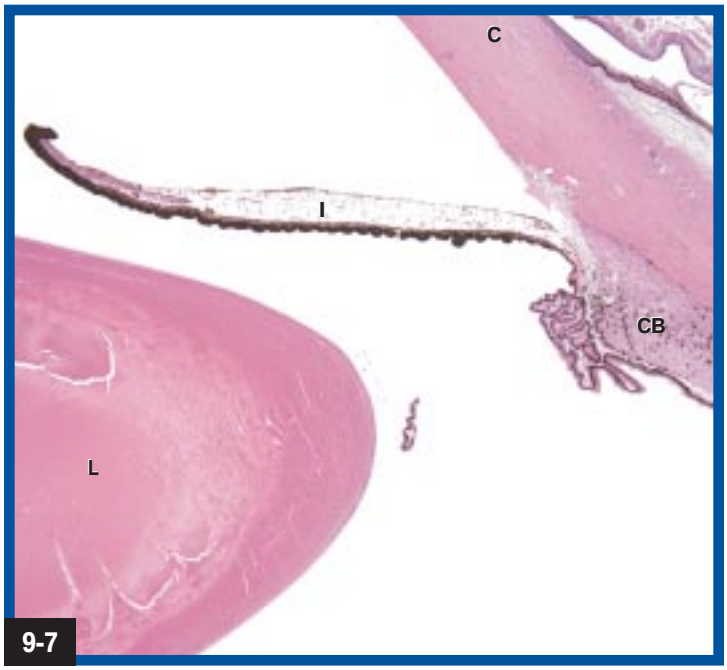
CORNEA The transparent anterior portion of the fibrous tunic is the cornea. There are five layers in the cornea. On the anterior surface is the corneal epithelium (C), a nonkeratinized stratified squamous epithelium. Bowman's membrane (B) is a collagenous basal lamina deep to the epithelium. The bulk of the cornea is the stroma (S), made of highly organized collagen fibers. Lastly, Descemet's membrane (D) and the simple squamous corneal endothelium (E) are posterior to the stroma. *(X60)*



CANAL OF SCHLEMM A venous sinus known as the canal of Schlemm (cS) is at the junction of the cornea (C) and sclera (S). It returns aqueous humor from the anterior chamber to the blood stream. *(X60)*



CHOROID The vascular tunic is made up of the choroid (C), a pigmented layer between the fibrous (F) and neural (N) tunics. *(X250)*



CILIARY BODY In the anterior of the eye, the vascular tunic is expanded to form the ciliary body (CB). Also visible are the cornea (C), iris (I), and lens (L). *(X20)*

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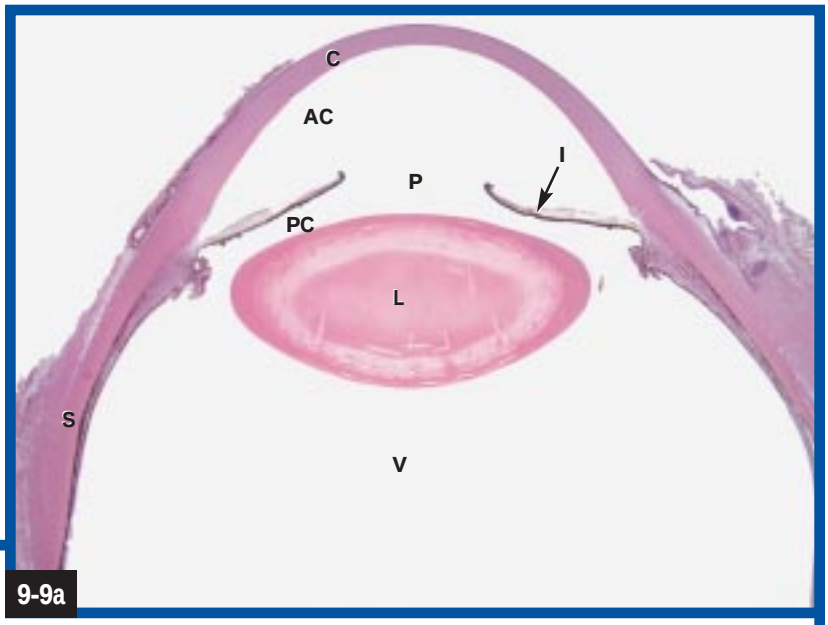
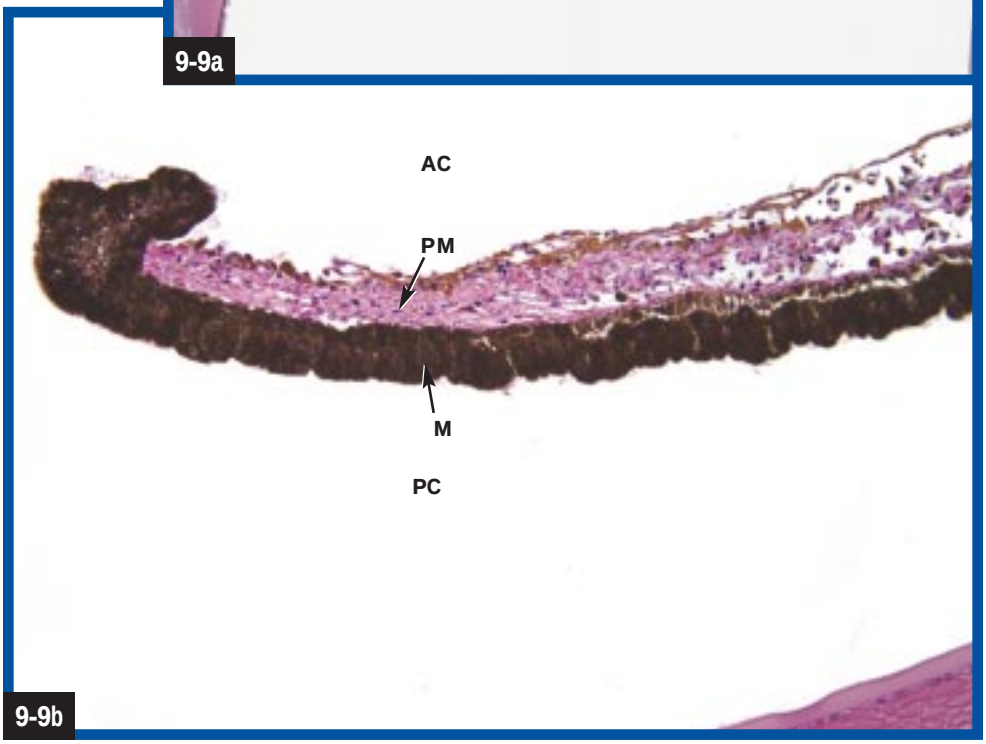
CILIARY PROCESSES Ciliary processes (CP) are extensions of the ciliary body (CB) that produce aqueous humor. The space (*) is an artifact of preparation where the sclera (S) has separated from the ciliary body. *(X100)*





IRIS (a) The iris (I) divides the anterior cavity into an anterior chamber (AC) and a posterior chamber (PC). Also visible are the lens (L), pupil (P), sclera (S), cornea (C), and the posterior cavity with the vitreous body (V). *(X6)* (b) This micrograph shows the iris in detail. Visible is the layer of melanocytes (M) on the posterior and the pupillary muscle (PM) within. *(X125)*

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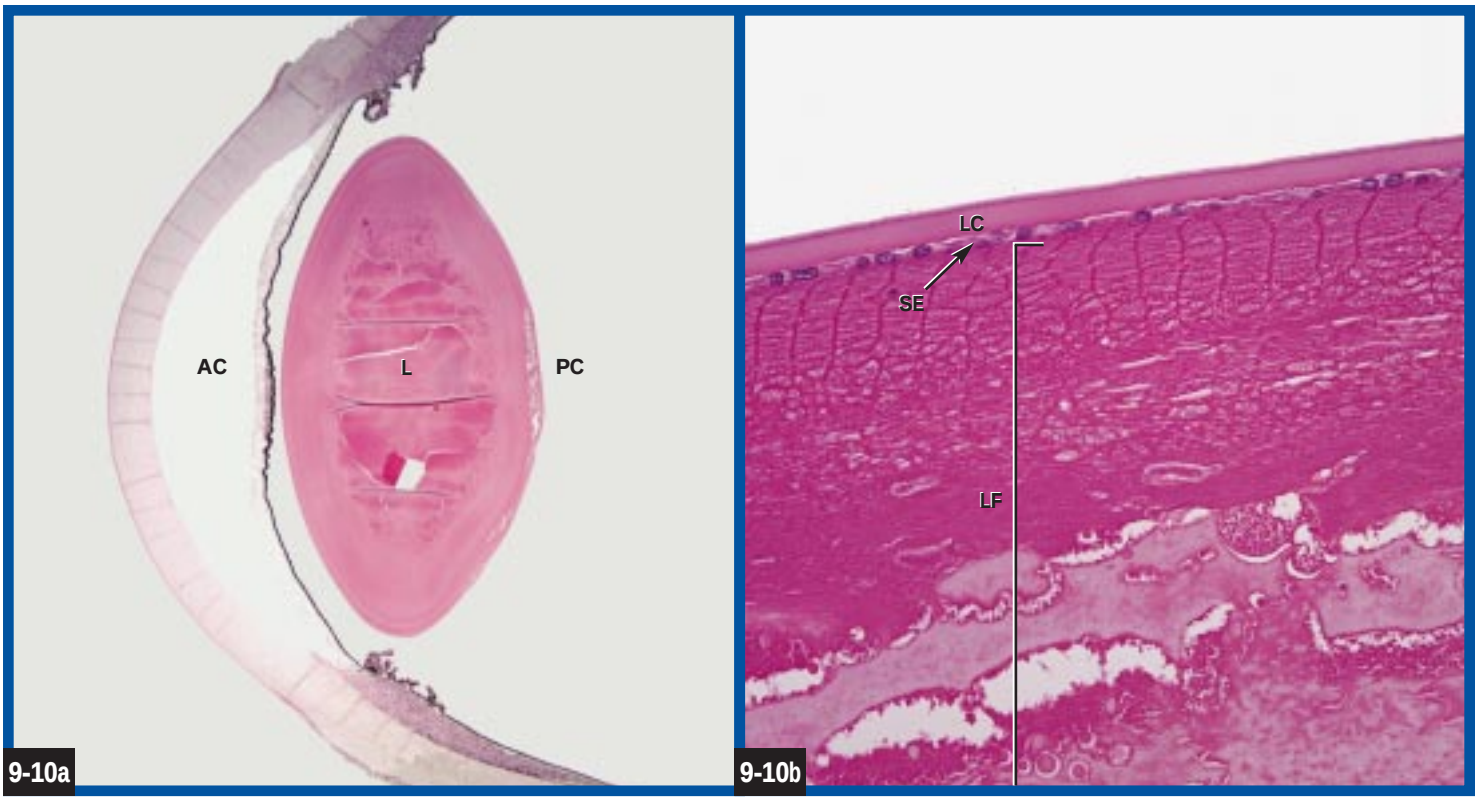
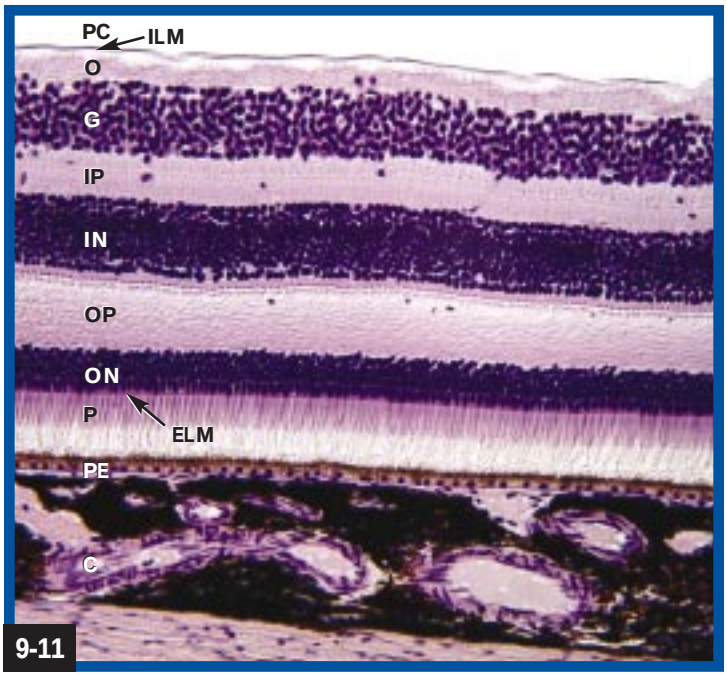
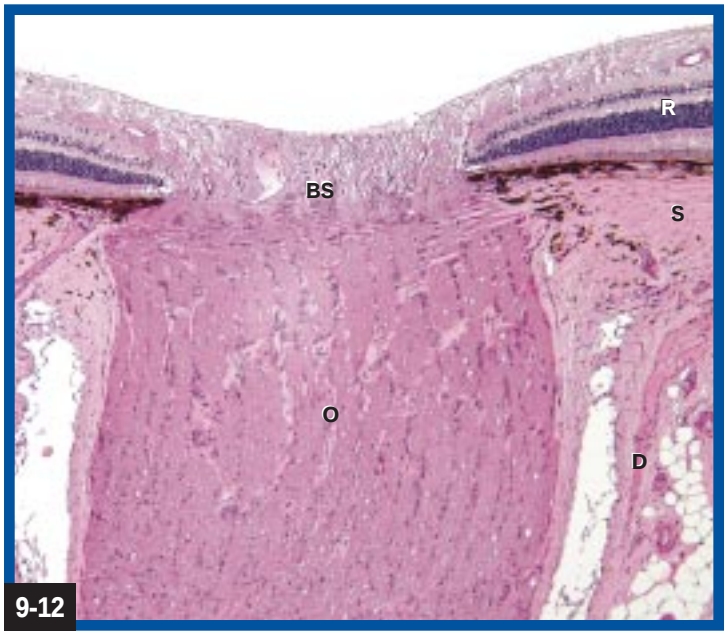


LENS (a) The lens (L) divides the eye into anterior (AC) and posterior cavities (PC). In this micrograph, suspensory ligaments are not visible. The iris also appears to lack a pupil, but this is due to the plane of the section. *(X7)* (b) In this higher magnification of the lens, the lens capsule (LC), subcapsular epithelium (SE), and lens fibers (LF) are visible. *(X250)*



RETINA The posterior cavity (PC) is at the top of this micrograph and the choroid (C) is at the bottom. In between is the retina. The ten layers of the retina are labeled as follows: **PE** = pigmented epithelium, **P** = photoreceptive layer (rod and cone segments), **ELM** = external limiting membrane, **ON** = outer nuclear layer, **OP** = outer plexiform layer, **IN** = inner nuclear layer, **IP** = inner plexiform layer, **G** = ganglion cell layer, **O** = optic nerve fiber layer, **ILM** = inner lining membrane. *(X125)*



OPTIC NERVE Where the optic nerve (O) leaves the posterior of the eye, there is no retina (R). This results in a blind spot (BS) in each eye. Notice that the sclera (S) is continuous with the dura mater (D) of the optic nerve. (As an outgrowth of the brain, the optic nerve is better referred to as the optic tract, so it is covered with dura mater, not epineurium.)

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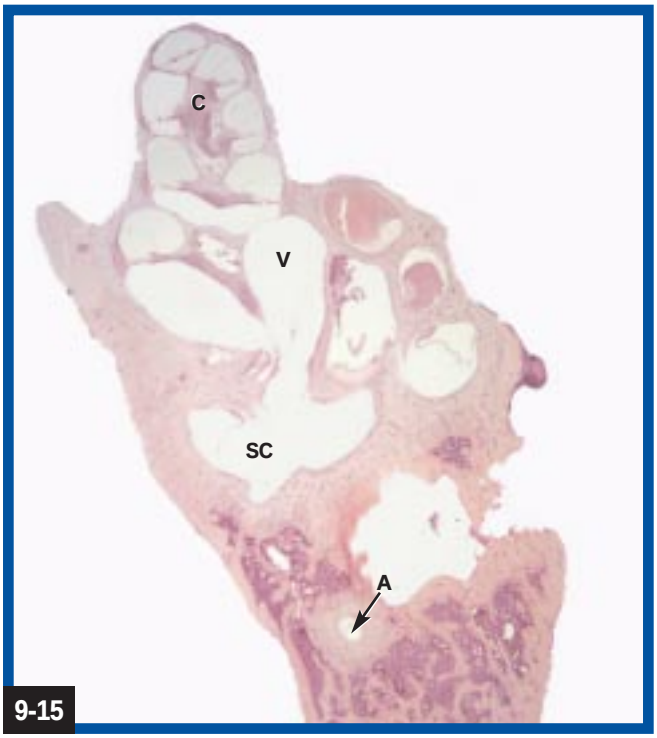
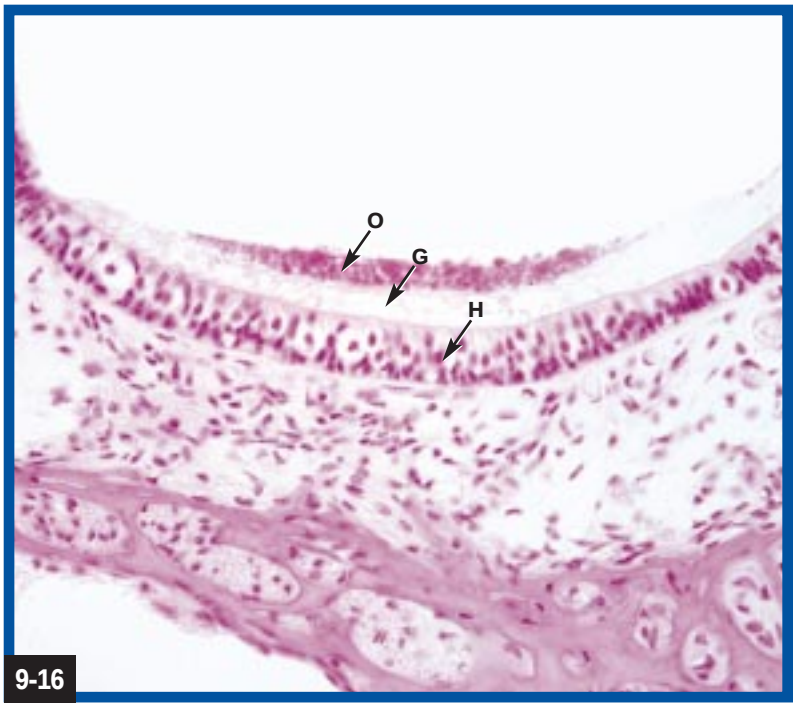
EYELID The eyelid is covered with a highly folded thin skin (S) on its anterior and a stratified columnar epithelium, the conjunctiva (C), on its posterior. The skeletal muscle (M), fibrous tarsal plate (T), and tarsal (Meibomian) glands (G) are also visible. *(X25)*

PINNA The external ear is covered with skin (S) which is tightly bound to an internal framework of elastic cartilage (E). Numerous hair follicles are also visible (arrows). *(X65)*



INTERNAL EAR This section of temporal bone shows much of the inner ear, a complex collection of cavities. The cochlea (C), semicircular canals (SC), and vestibule (V). Also shown is the auditory tube (A). *(X8)*



MACULA The vestibule of the inner ear houses the membranous utricle and saccule, each with a macula. This micrograph shows a macula with otoliths (O) embedded in a glycoprotein (G) layer that covers the receptive hair cells (H). The macula provides sensory information about head position. *(X250)*

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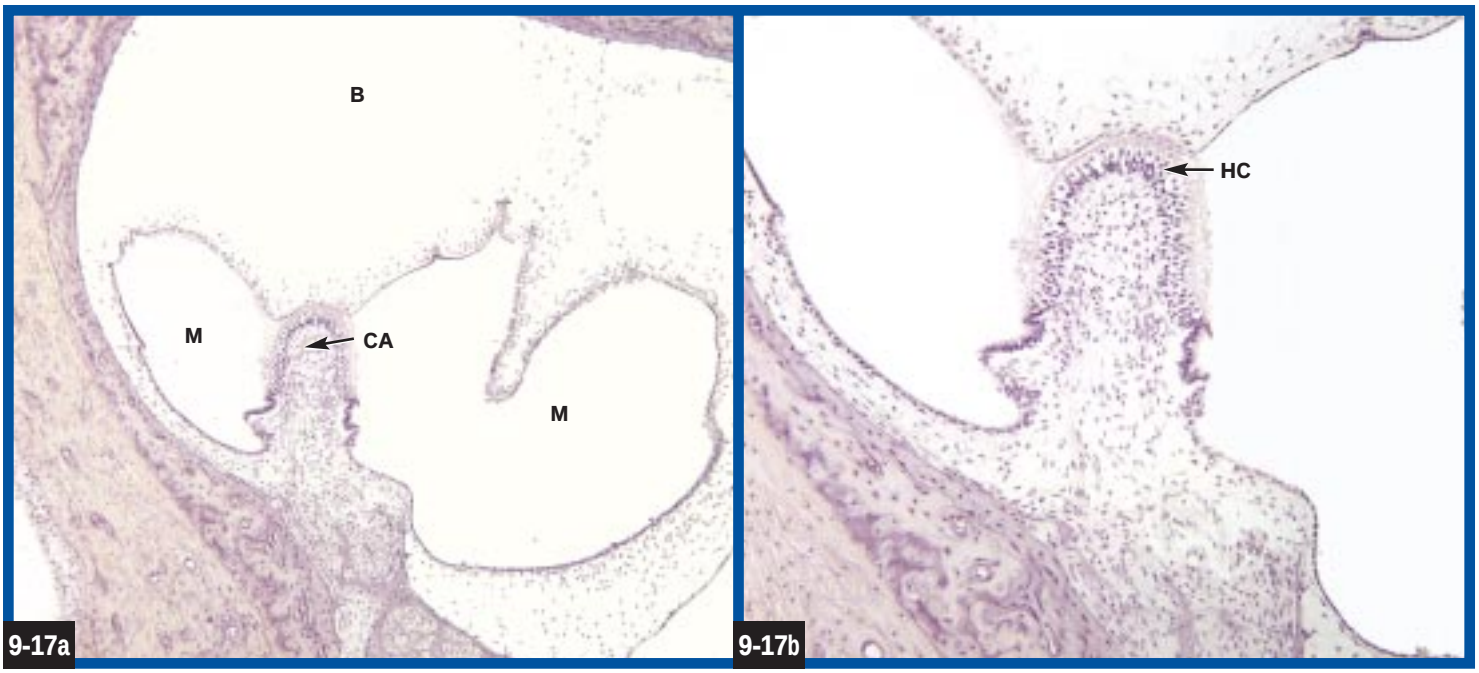

AMPULLA OF A SEMICIRCULAR CANAL Each of the three semicircular canals has a dilated end called the ampulla. Within the ampulla is the crista ampullaris, a receptor organ that provides sensory information about body movement. (a) The bony (B) and membranous (M) labyrinths of the vestibule are labeled in this micrograph. Note that the membrane is unnaturally collapsed due to preparation of the specimen. The crista ampullaris (CA) is also visible. *(X50)* (b) In this detail of the crista ampullaris, the hair cell layer (HC) is visible, but much of the cupula (the glycoprotein layer covering the crista) is missing. *(X100)*

DETAIL OF COCHLEA The membranous labyrinth is represented by the scala media (SM), which is separated from the bony labyrinth by the vestibular membrane (V) and basilar membrane (B). The bony labyrinth consists of the scala vestibuli (SV) and scala tympani (ST). The organ of Corti (O) rests on the basilar membrane. *(X100)*

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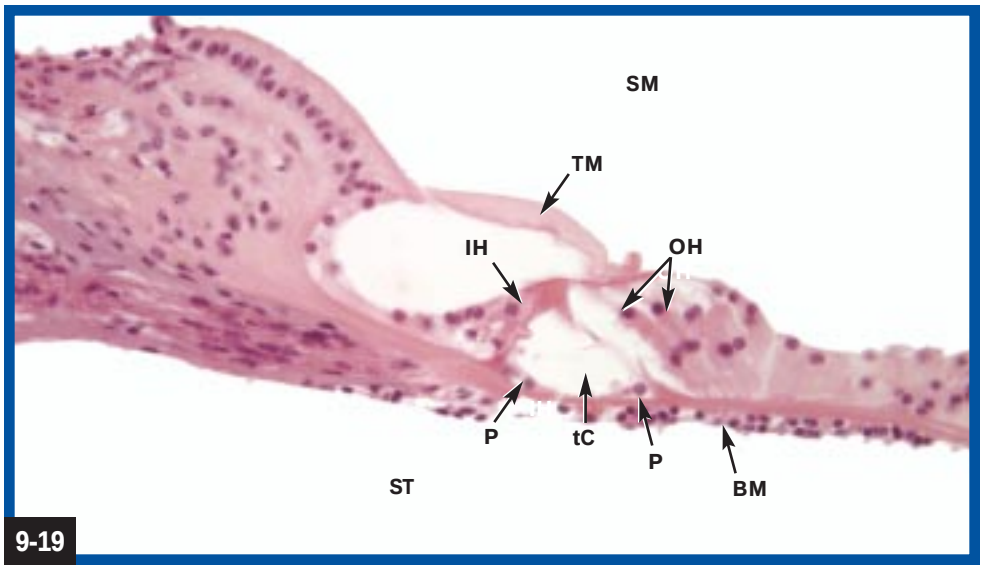
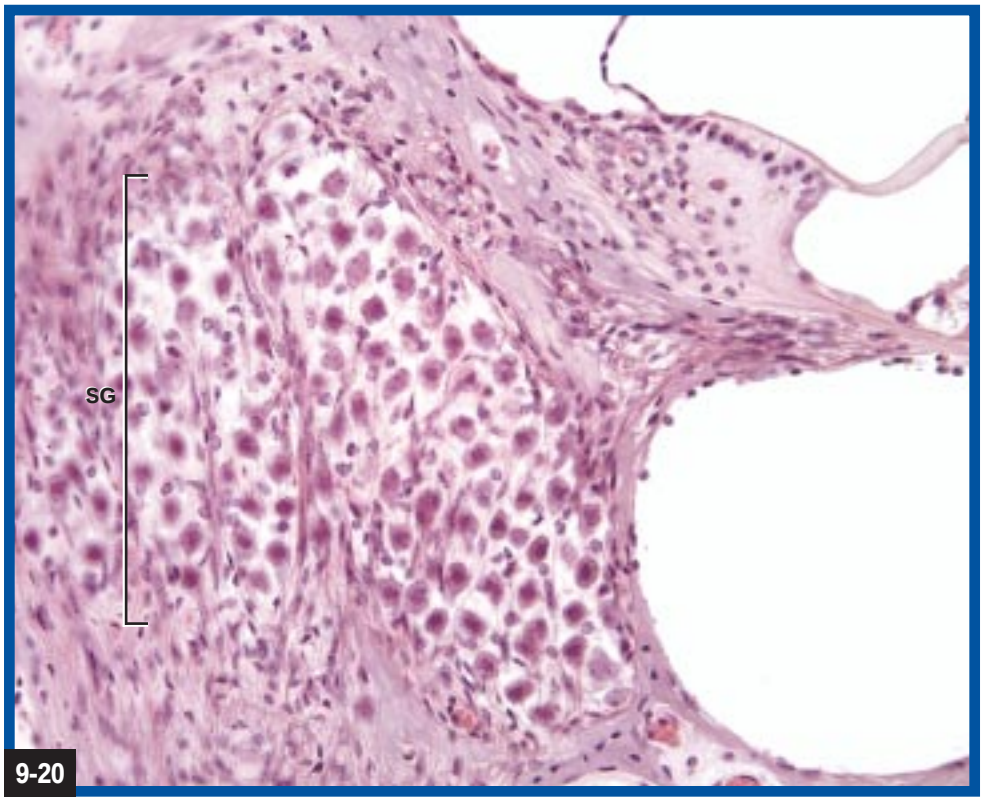


ORGAN OF CORTI The organ of Corti is the receptor for the sensation of hearing. The actual receptors are hair cells, of which there are two types: an inner hair cell (IH) and outer hair cells (OH). Other parts of the organ of Corti, such as pillar cells (P), other support cells, tunnel of Corti (tC), basilar membrane (BM) and the tectorial membrane (TM) are also visible. The scala media (SM) is above the organ of Corti and the scala tympani (ST) is below it. *(X250)*



SPIRAL GANGLION The nerve cell bodies whose axons form the auditory nerve are located in spiral ganglia (SG) within the modiolus. They transmit sensory impulses from the hair cells to the cerebral cortex to produce the sensation of hearing. *(X250)*

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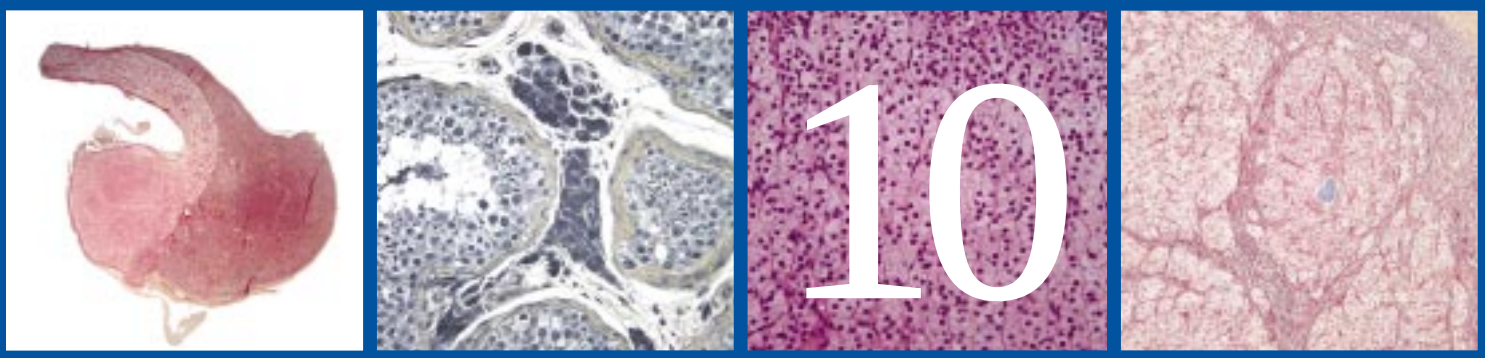
Endocrine System

CHAPTER 10



Introduction to the Endocrine System

The endocrine system is composed of **endocrine glands** and **endocrine cells**. The former are multicellular organs, and the latter are cells dispersed within organs with more than an endocrine function.

Endocrine glands are typically epithelial in origin and are produced as a result of surface cells growing down into deeper tissues. Unlike exocrine glands that maintain their connection with the surface (by way of their duct), the connection of endocrine glands is lost during development and the glands are "ductless." Each gland produces one or more peptide or lipid hormones, which are secreted into the blood stream. For this reason, endocrine glands are very vascular. The hormones have a physiological effect on specific **targets**, cells in organs elsewhere in the body. In this way, the endocrine system regulates activities in concert with the nervous system.

Endocrine glands are structurally diverse, but they do have some general features in common. The secretory cells are referred to as **parenchyma**. There is also often a connective tissue **capsule** and, of course, the numerous capillaries into which hormones are secreted.

Endocrine glands covered in this chapter are the pituitary gland, thyroid gland, parathyroid glands, adrenal glands, pineal gland, pancreas, testes, and ovaries.

Pituitary Gland (Hypophysis)

The pituitary gland is located inferior to the hypothalamus and occupies the sella turcica of the sphenoid bone. It is about the size of a garden pea. Its three parts have two different embryological origins: the **adenohypophysis (anterior pituitary)** and **pars intermedia** are derived from oral ectoderm, and the **neurohypophysis (posterior pituitary)**, which is an outgrowth of the hypothalamus (Figure 10-1).

Adenohypophysis (Anterior Pituitary)

Two main cell types are recognized in the adenohypophysis using traditional staining methods. These are the easily stained **chromophils** and the poorly staining **chromophobes** (Figure 10-2). Chromophils are further differentiated into **acidophils** and **basophils**, depending on their affinity for acidic and basic stains, respectively. Immunohistochemical techniques have resulted in categorizing these cells based on their secretion. **Somatotrophs** and **mammotrophs** secrete growth hormone (GH) and prolactin, respectively, and are acidophils. The basophilic **corticotrophs**, **thyrotrophs**, and **gonadotrophs** secrete adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), and follicle stimulating hormone (FSH) and luteinizing hormone (LH), respectively.

Chromophobes are thought to be chromophils that have discharged their secretory granules (*i.e.*, degranulated).

Neurohypophysis (Posterior Pituitary)

The neurohypophysis consists of unmyelinated fibers of neurosecretory cells whose cell bodies are located in the hypothalamus (Figure 10-3). Glial-like **pituicytes** support the fibers.

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Pars Intermedia and Pars Tuberalis

The **pars intermedia** consists of basophilic cells located between the anterior and posterior pituitary and is visible in some specimens. Small cysts with acidophilic colloidal material characterize it and produce melanocyte stimulating hormone.

The **pars tuberalis** is found associated with the **infundibular stalk** of the pituitary. Its function is not known.

Thyroid Gland

The **thyroid gland** is found anterior to the larynx in the neck. It is composed of two lobes and is surrounded by a thin **capsule**. Connective tissue **septa** divide the thyroid gland into **lobules**.

Unlike most endocrine glands, the thyroid does not store its secretion intracellularly. Rather, the inactive hormones are stored in the lumina of **thyroid follicles** (Figure 10-4). Each follicle is formed by a simple cuboidal epithelium that produces the hormones T_3 and T_4, which are responsible for regulating metabolic rate. In addition, the much less abundant **clear** (**C**) **cells** produce the hormone calcitonin, which regulates blood calcium levels.

Parathyroid Glands

The **parathyroid glands** are located on the posterior of the thyroid gland. Each is enclosed by a fibrous **capsule** that sends **septa** into the gland and divides it into **lobules** (Figure 10-5). Parathyroid hormone is involved in regulating blood calcium and phosphate levels.

The parenchyma is composed of hormone secreting **chief cells** and **oxyphil cells** of unknown function. Chief cells are small with round, centrally positioned nuclei and pale, eosinophilic cytoplasm. Oxyphils are larger with an abundance of eosinophilic cytoplasm.

Adrenal Glands

The **adrenal glands** are located superior to each kidney. They consist of a fibrous **capsule** surrounding the parenchyma, which is divided into an outer cortex and an inner **medulla** (Figure 10-6a).

The adrenal cortex is divided into three layers. The **zona glomerulosa** (Figure 10-6b) is a thin layer deep to the capsule. Its cells are in rounded clusters and have dense staining nuclei. They secrete the mineralocorticoid hormone aldostrerone, which increases blood pressure by increasing sodium reabsorption in the kidney tubules. The **zona fasciculata** (Figure 10-6c) is deep to the zona glomerulosa and is the thickest of the three cortical layers. Its cells are arranged in rows and are called **spongiocytes** (Figure 10-6d) due to their appearance from the abundant cytoplasmic lipids. The main hormone is cortisol, which raises blood glucose levels among other metabolic effects. The **zona reticularis** (Figure 10-6e) is the innermost cortical layer. The nuclei and cytoplasm of its cells stain more intensely than the spongiocytes. These cells secrete small amounts of sex hormones.

The adrenal medulla (Figure 10-7) is essentially a ganglion of the sympathetic nervous system. Its cells are the developmental and functional equivalents of sympathetic postganglionic neurons. They secrete the hormones epinephrine and norepinephrine that act along with direct sympathetic innervation to prepare the body for dealing with stressful situations. The secretory cells are basophilic and have large nuclei.

Pineal Gland

The **pineal gland** is a small outgrowth from the roof of the third ventricle (Figure 10-8). Modified neurons called **pinealocytes** secrete the hormones melatonin and serotonin, and are characterized by round nuclei with prominent nucleoli. **Interstitial cells**, which are structurally and functionally similar to astrocytes, are found surrounding clusters of pinealocytes. **Pineal sand (corpora arenacea)**, made of calcium phosphate and calcium carbonate, becomes more abundant with age, but is of unknown function.

Pancreas

The **pancreas** has endocrine and exocrine components. **Islets of Langerhans** comprise the endocrine portion (Figure 10-9). The majority of cells (up to 70%) in an islet are the insulin secreting β **cells**. The glucagon secreting α **cells** are toward the periphery of the islet and comprise about 20% of the cells. These hormones decrease and increase blood sugar levels, respectively. The remaining cells are of three types, defined by their secretions: somatostatin, gastrin, and pancreatic polypeptide. Typical histological stains do not distinguish between the five different cells that manufacture and secrete each chemical, but they can be differentiated with immunocytochemical stains specific for their secretions.

Testes

The testes have a cytogenic function (sperm production) and an endocrine function. The **interstitial cells of Leydig** are located in the vascular connective tissue between seminiferous tubules of the testes (Figure 10-10). They are responsible for secretion of testosterone, the male sex hormone. The cells have a round nucleus with one or two eccentric nucleoli and lipids in the cytoplasm.

Ovaries

Like the testes, ovaries have a cytogenic and an endocrine function. As ovarian follicles develop (Figure 10-11), the ovum undergoes meiosis and the surrounding follicle cells proliferate. The **thecal cells** of developing ovarian follicles produce estrogen, one of the female sex hormones. After ovulation, the ovarian follicle undergoes changes and develops into a **corpus luteum** (Figure 10-12). The **granulosa**

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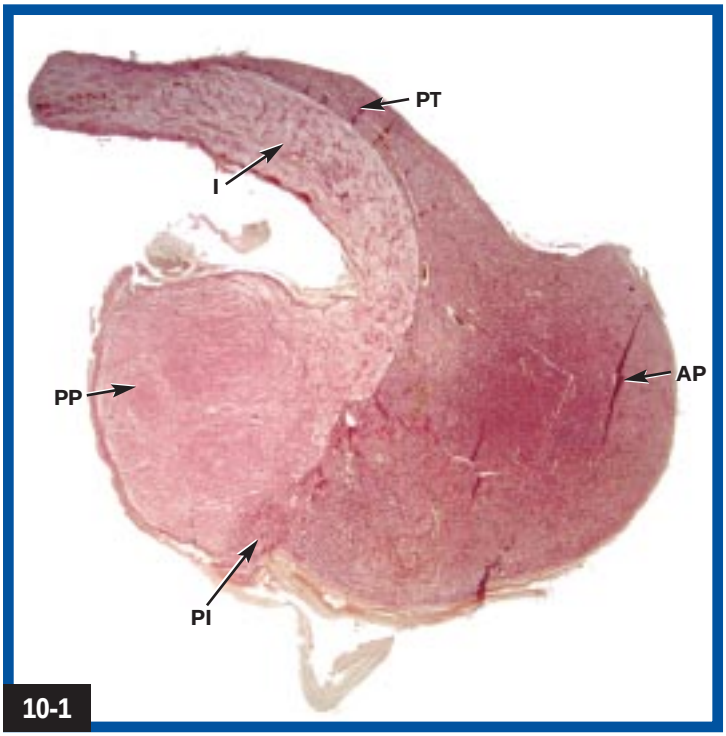
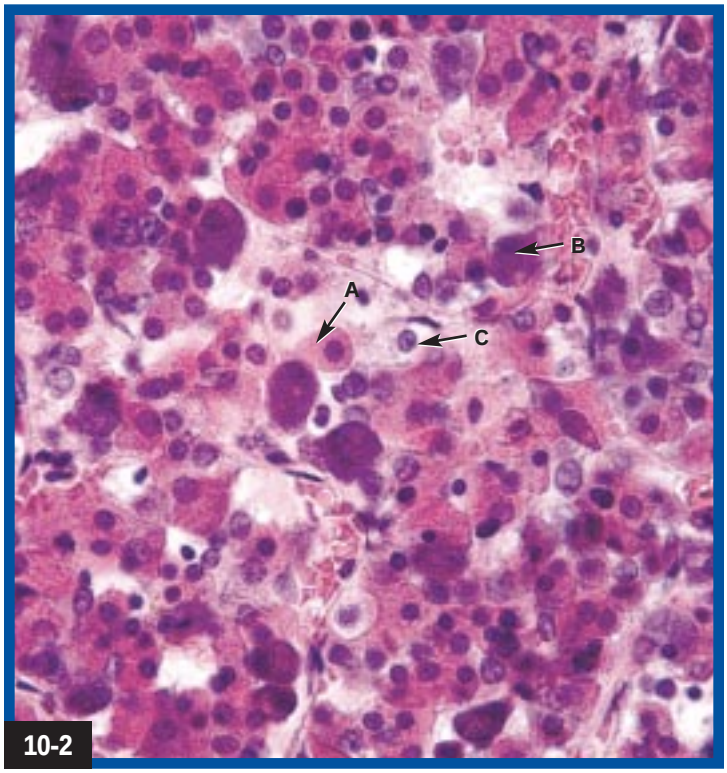
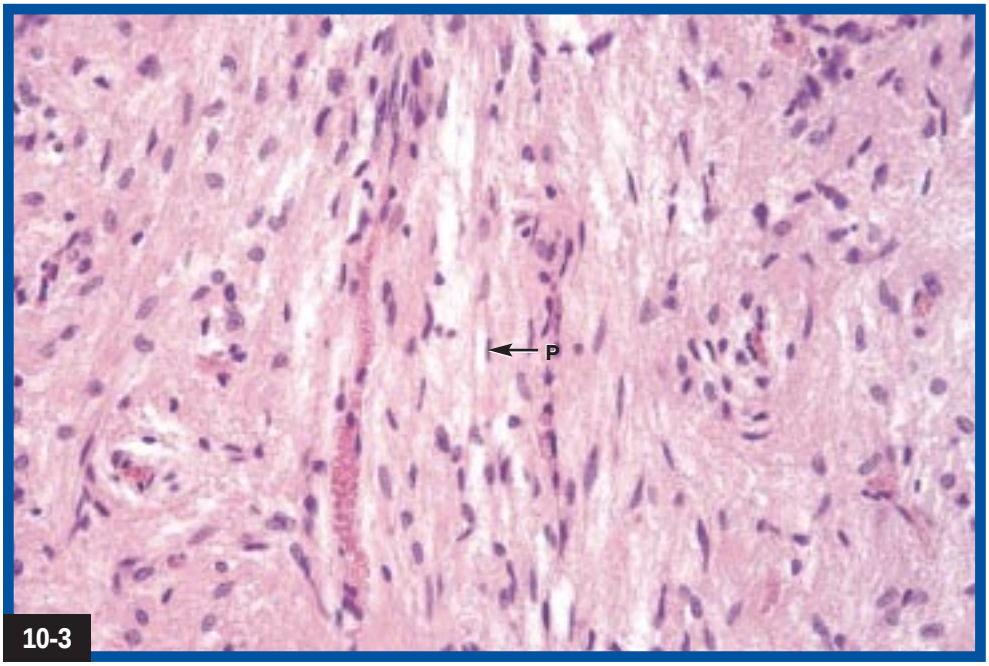
lutein cells secrete progesterone and some estrogen. If pregnancy occurs, the corpus luteum continues growing and secreting hormones for the first trimester, after which it degenerates and the placenta assumes the role of hormone production. If pregnancy does not occur, the corpus luteum degenerates approximately within two weeks of ovulation.



PITUITARY GLAND The drastically different appearances of the anterior pituitary (AP) and posterior pituitary (PP) are consistent with their different embryonic origins. The anterior pituitary develops from oral ectoderm, whereas the posterior pituitary grows from the hypothalamus. Also visible are the infundibular stalk (I), pars tuberalis (PT), and pars intermedia (PI). *(X7)*



ANTERIOR PITUITARY GLAND The secretory cells of the anterior pituitary gland can be differentiated with H&E stain into chromophils, which stain intensely, and chromophobes (C), which don't. The former can further be differentiated into reddish acidophils (A) and purplish basophils (B). Further identification requires immunohistochemical staining for the specific hormones. Note the numerous blood vessels surrounding the secretory cells. *(X380)*



POSTERIOR PITUITARY The bulk of the posterior pituitary is composed of unmyelinated fibers from neurons in the hypothalamus. These are supported by glial-like pituicytes (P). *(X250)*

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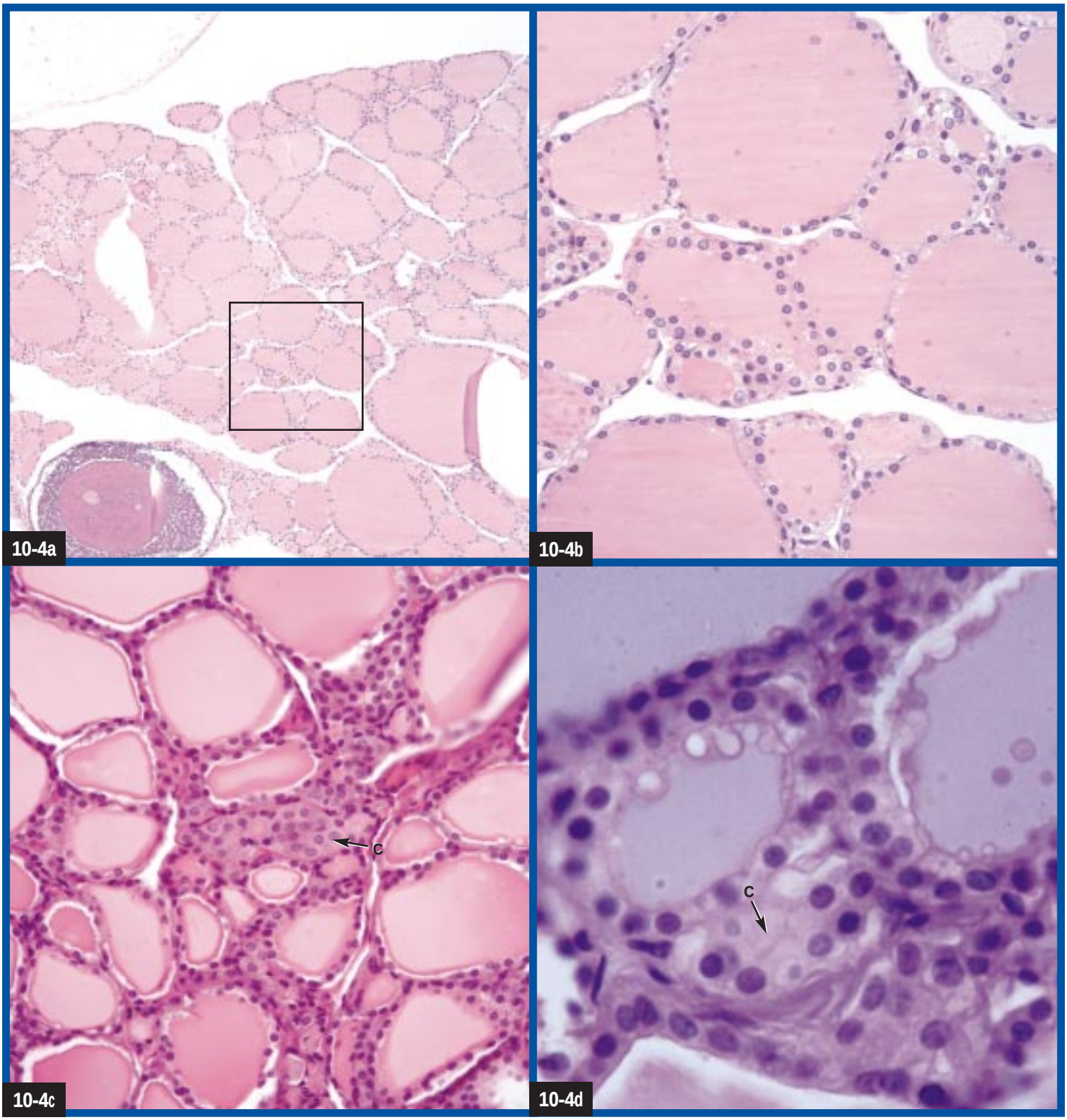

THYROID GLAND (a) The follicular nature of the thyroid gland is apparent in this micrograph. *(X65)* (b) This is a higher magnification of the boxed region in (a). Each follicle is made of simple cuboidal cells that secrete inactive thyroid hormones into its lumen. *(X250)* (c) Larger and paler staining clear cells (C) are found between follicles. They secrete calcitonin, a hormone involved in regulating blood calcium levels. *(X250)* (d) This is a higher magnification of clear cells. Notice the thyroid follicles surrounding them. *(X380)*

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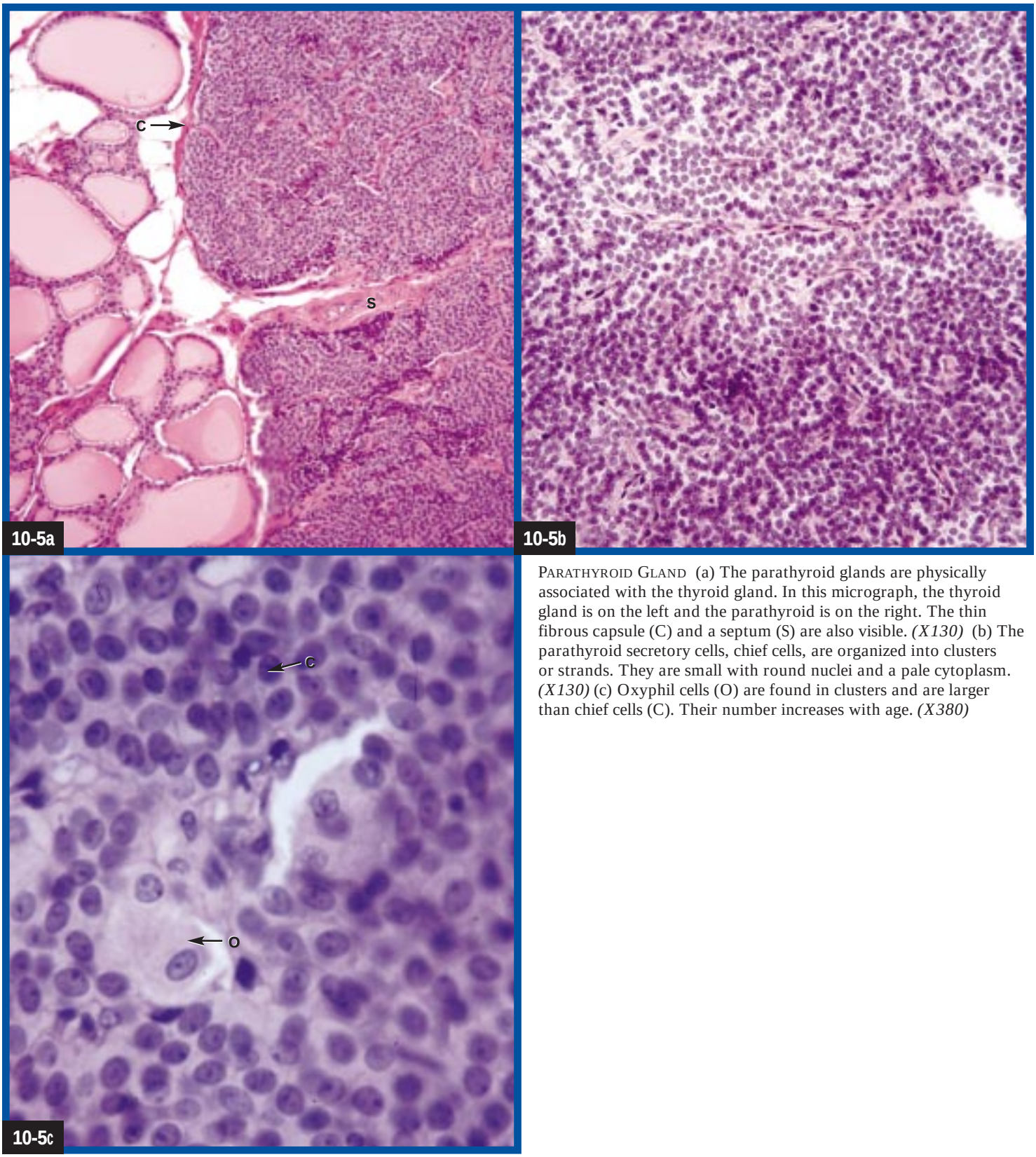

PARATHYROID GLAND (a) The parathyroid glands are physically associated with the thyroid gland. In this micrograph, the thyroid gland is on the left and the parathyroid is on the right. The thin fibrous capsule (C) and a septum (S) are also visible. *(X130)* (b) The parathyroid secretory cells, chief cells, are organized into clusters or strands. They are small with round nuclei and a pale cytoplasm. *(X130)* (c) Oxyphil cells (O) are found in clusters and are larger than chief cells (C). Their number increases with age. *(X380)*

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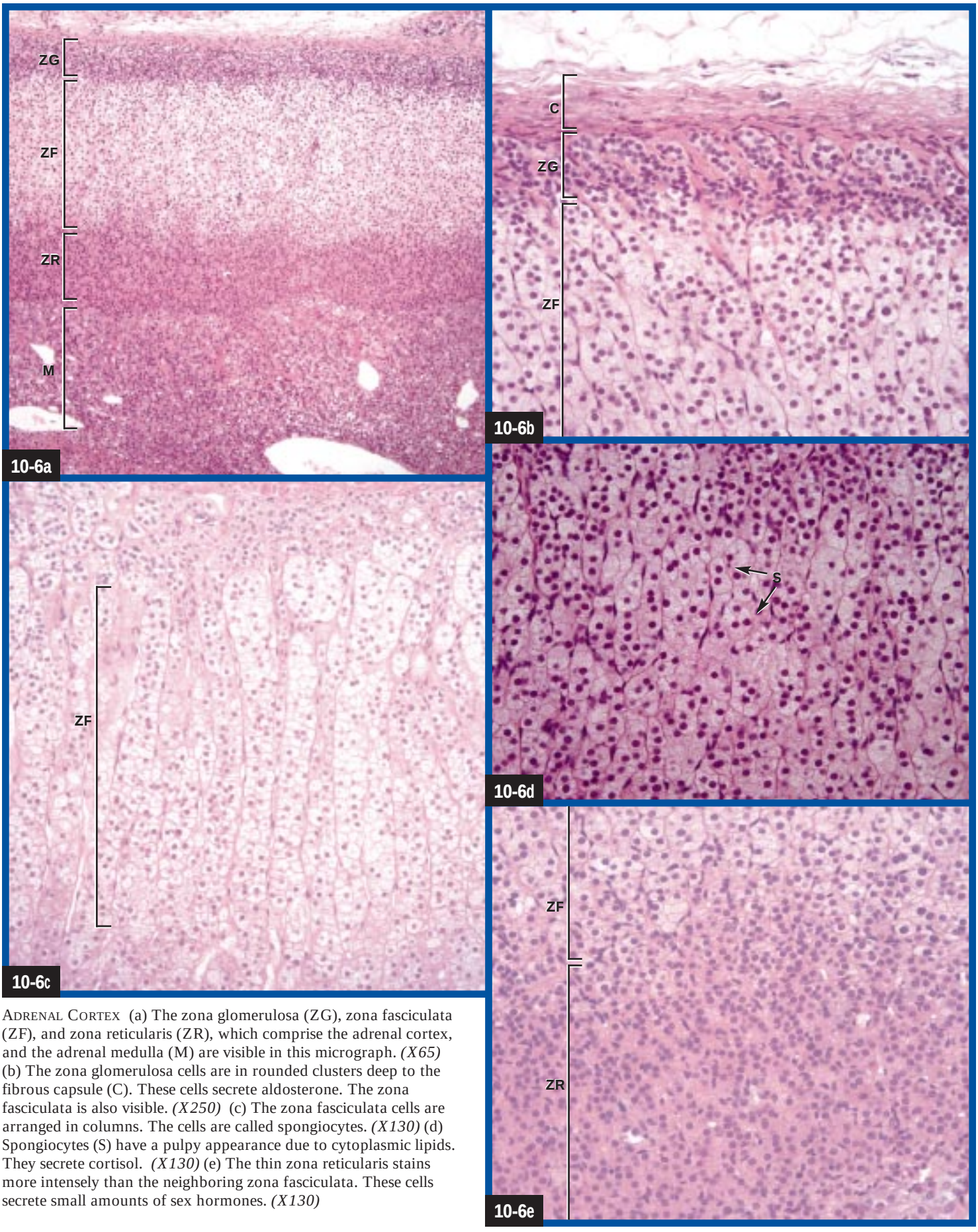

ADRENAL CORTEX (a) The zona glomerulosa (ZG), zona fasciculata (ZF), and zona reticularis (ZR), which comprise the adrenal cortex, and the adrenal medulla (M) are visible in this micrograph. *(X65)* (b) The zona glomerulosa cells are in rounded clusters deep to the fibrous capsule (C). These cells secrete aldosterone. The zona fasciculata is also visible. *(X250)* (c) The zona fasciculata cells are arranged in columns. The cells are called spongiocytes. *(X130)* (d) Spongiocytes (S) have a pulpy appearance due to cytoplasmic lipids. They secrete cortisol. *(X130)* (e) The thin zona reticularis stains more intensely than the neighboring zona fasciculata. These cells secrete small amounts of sex hormones. *(X130)*

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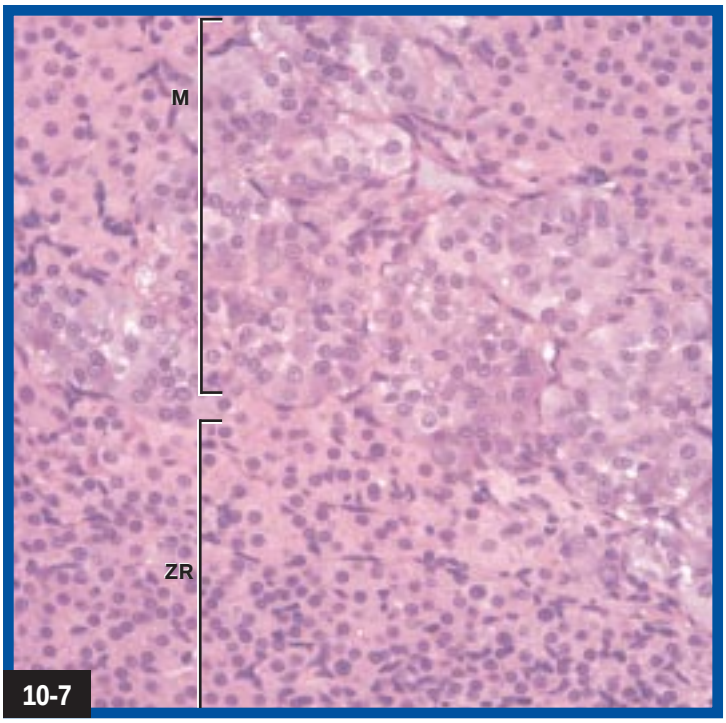
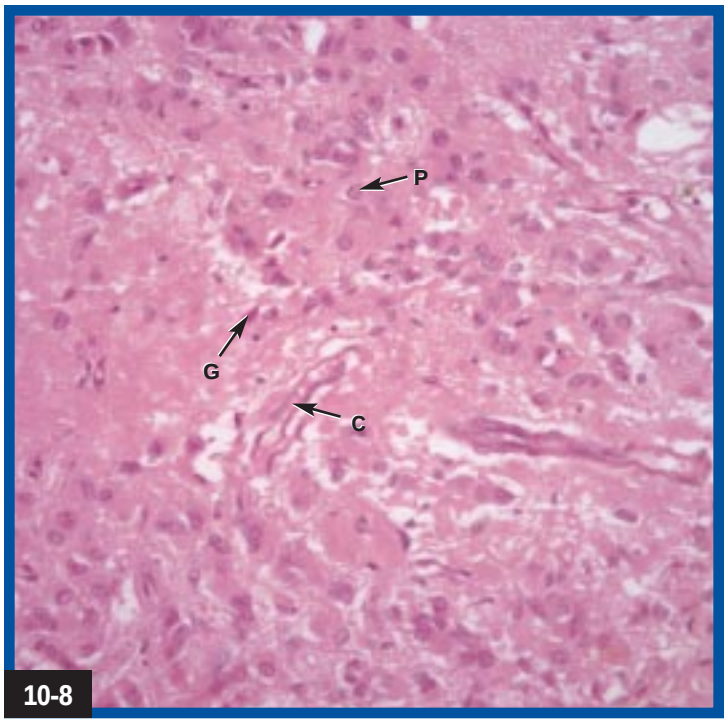
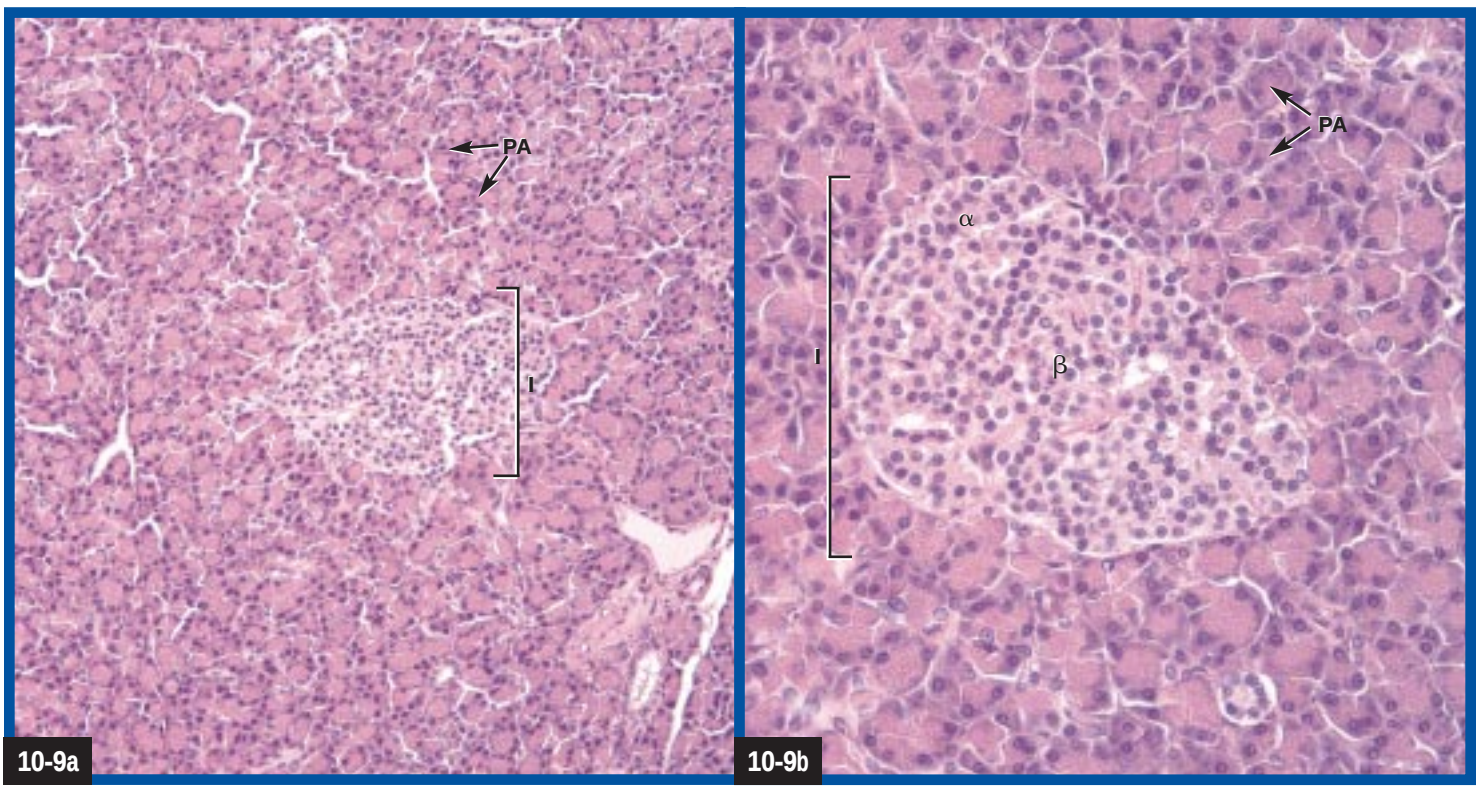


ADRENAL MEDULLA The cells of the adrenal medulla (M) are modified neurons that secrete epinephrine and norepinephrine. It is found at the core of the adrenal gland. Note the zona reticularis (ZR) surrounding the adrenal medulla. *(X130)*



PINEAL GLAND The pinealocytes (P) are modified neurons with a round nuclei and obvious nucleoli. They are arranged in clusters associated with numerous capillaries (C). Also present are glial cells (G). (*X250*)



PANCREAS (a) Islets of Langerhans (I) comprise the endocrine portion of the pancreas. Surrounding the islets are the exocrine pancreatic acini (PA). *(X135)* (b) Immunocytochemical stains allow recognition of five cell types in the islet, but H&E stains (used in this specimen) do not, so all cells look alike. Insulin secreting β cells (β) are the most abundant cells of the islet and tend to be located in the center. The α cells (α), which secrete glucagon, tend to be found near the periphery. *(X250)*

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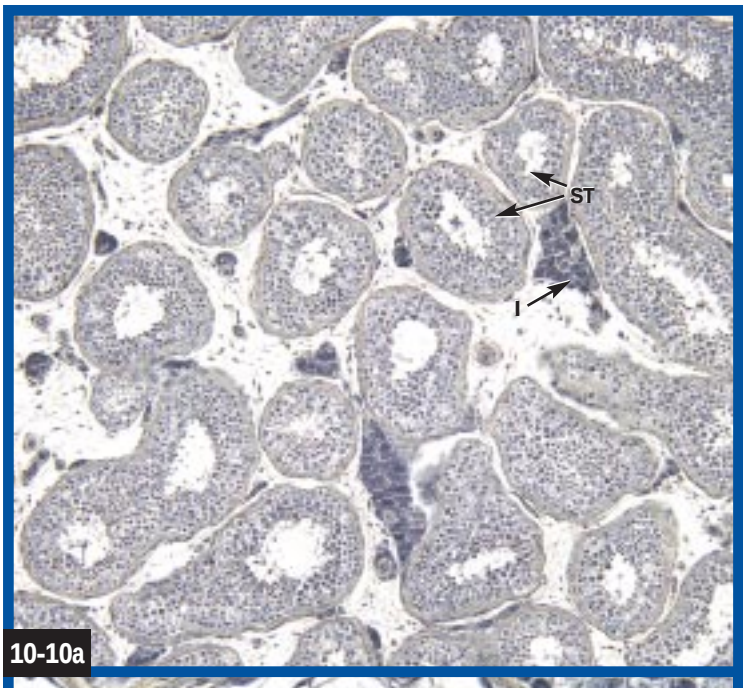
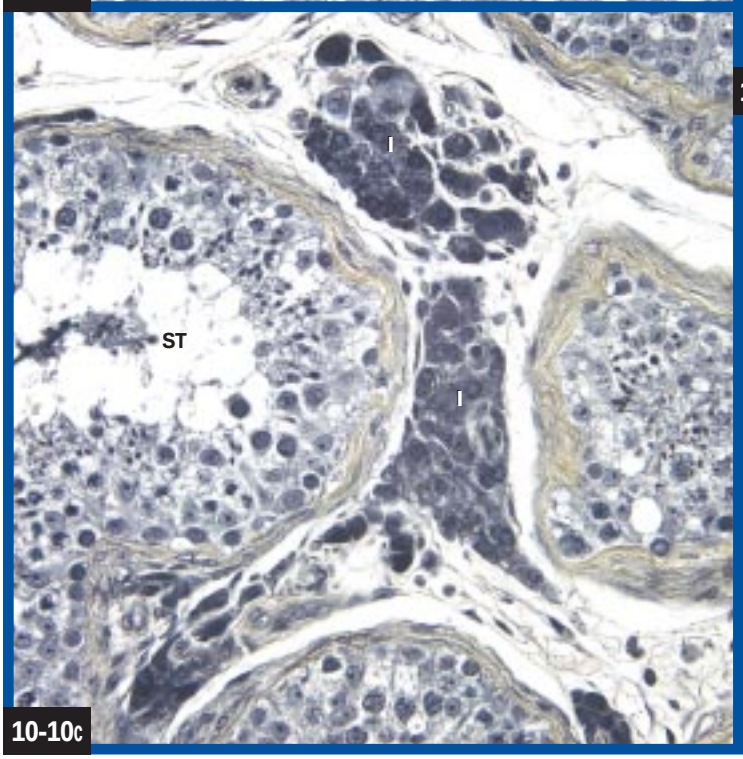


10-10a



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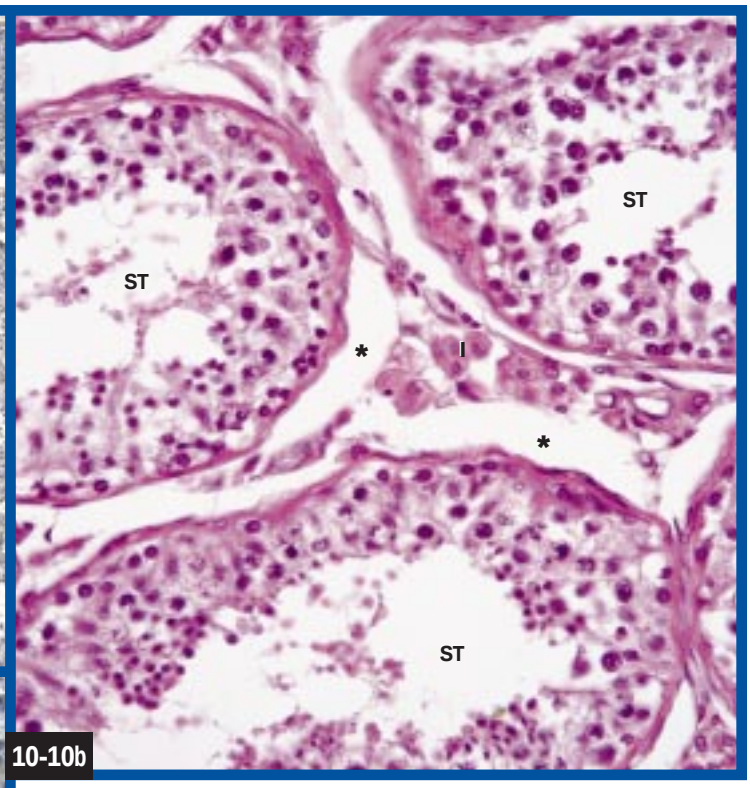
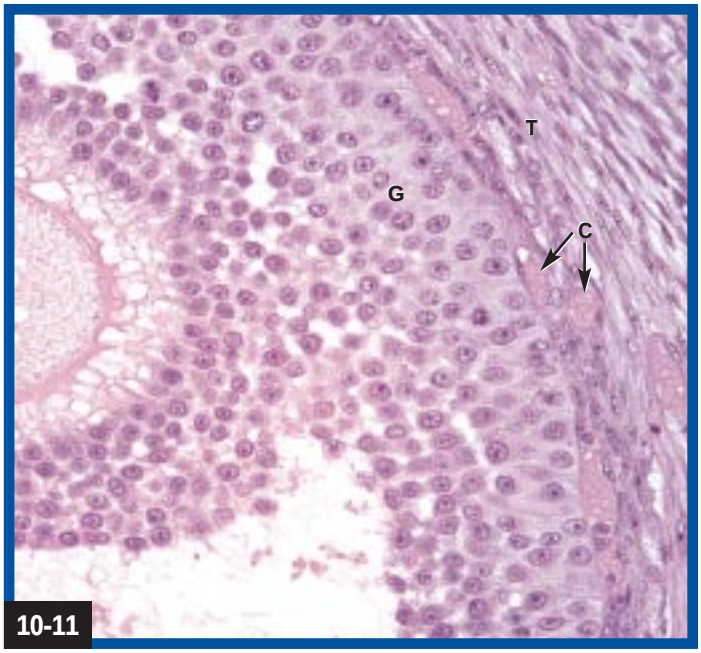


10-10b

TESTICULAR INTERSTITIAL CELLS OF LEYDIG (a) The interstitial cells (I) are found between seminiferous tubules (ST). *(X65)* (b) Interstitial cells (I) secrete testosterone and can be identified based on their location between seminiferous tubules and their obvious, eccentric nucleoli. The space (*) between the interstitial cells and the seminiferous tubules is an artifact of preparation. *(X250)* (c) This is another example of interstitial cells. These would have to be identified based on their position between seminiferous tubules, since nuclear staining is not very good. *(X250)*



10-11

OVARY THECAL AND GRANULOSA CELLS During development, thecal (T) and granulosa (G) cells in the ovarian follicle have an endocrine function and secrete estrogen. Note the abundance of capillaries (C). *(X250)*

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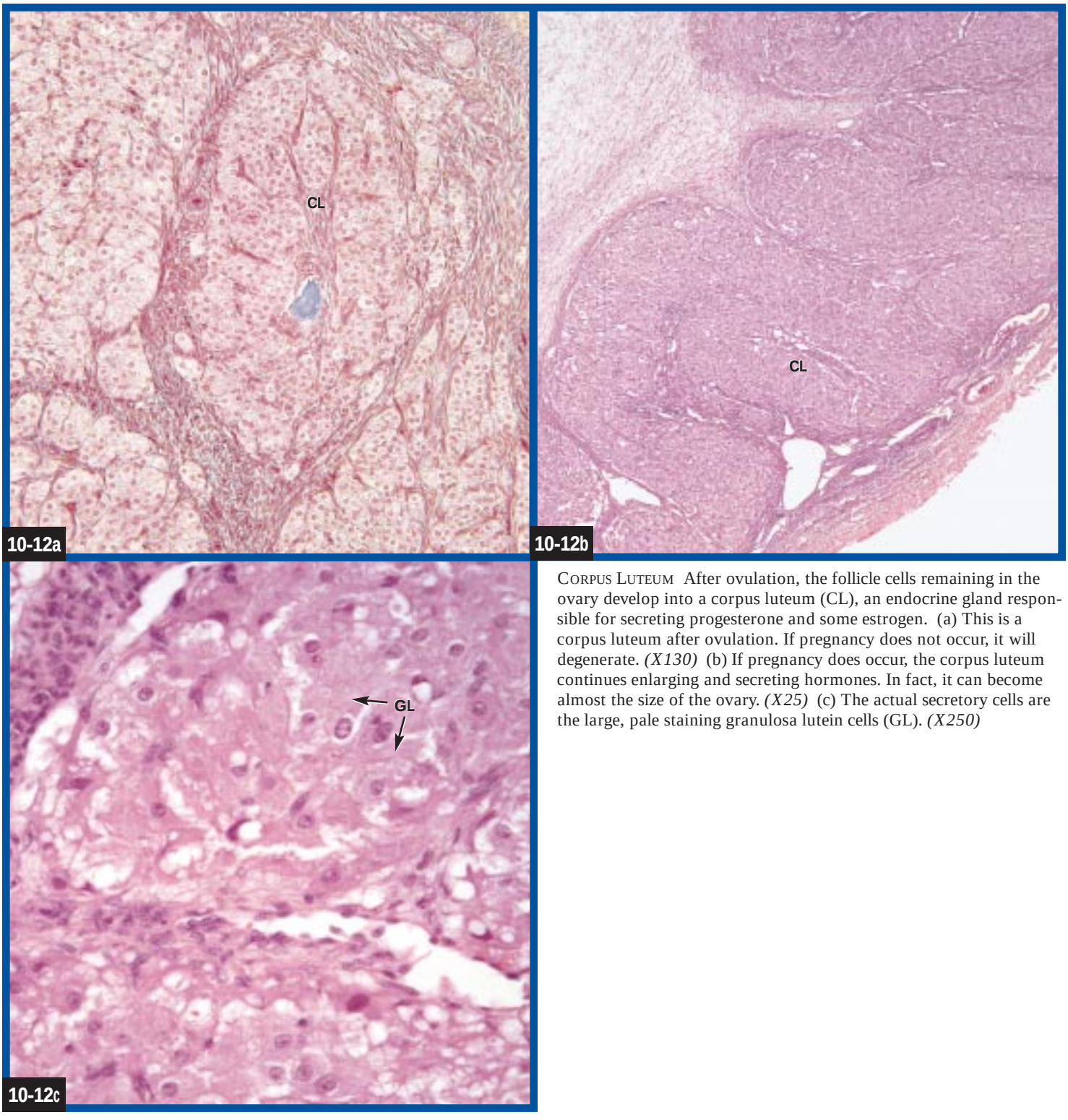

CORPUS LUTEUM After ovulation, the follicle cells remaining in the ovary develop into a corpus luteum (CL), an endocrine gland responsible for secreting progesterone and some estrogen. (a) This is a corpus luteum after ovulation. If pregnancy does not occur, it will degenerate. *(X130)* (b) If pregnancy does occur, the corpus luteum continues enlarging and secreting hormones. In fact, it can become almost the size of the ovary. *(X25)* (c) The actual secretory cells are the large, pale staining granulosa lutein cells (GL). *(X250)*

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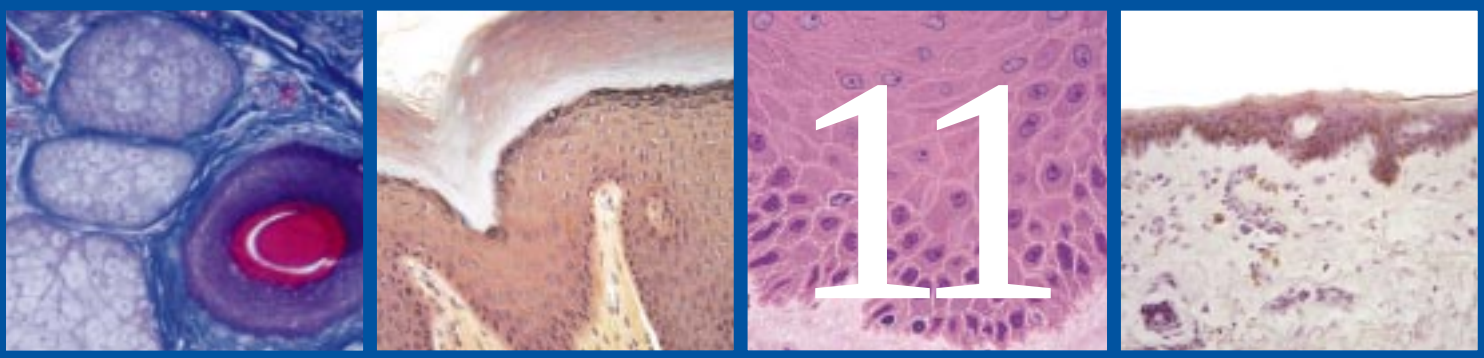
Integumentary System

CHAPTER



Introduction to the Integument

The integumentary system consists of the skin and its appendages, such as hair, nails, and various glands. It functions as a covering for the entire body. In this role, it protects against mechanical damage and presents a barrier to penetration by chemicals and infectious agents. It also is involved in sensation, thermoregulation (through sweat glands and regulating blood flow), and vitamin D synthesis.

It is the largest organ in the body. The average thickness of the skin is about 1 to 2 mm, but it tends to be thicker on dorsal surfaces than on ventral surfaces (the palms of the hands and soles of the feet are exceptions to this).

Layers of the Integument

The skin is composed of two layers: the superficial **epidermis** and the deeper **dermis** (Figure 11-1). Deep to the dermis is the **hypodermis**, also known as **superficial fascia**. Where it is replaced with adipose tissue, it is known as **subcutaneous fat**. While the hypodermis is not part of the integument, it will be covered in this chapter since it is visible on most skin slides and some epidermal appendages penetrate it.

Epidermis

The epidermis is derived from ectoderm and is composed of keratinized stratified squamous epithelium. Its thickness ranges from 0.1 mm (over most of the body) to 1.4 mm (on the soles of the feet). Figure 11-2 illustrates thick and thin skin.

The main epidermal cells are called **keratinocytes**. The basal cells are the healthiest due to their proximity to the dermal capillaries, and they are the ones that undergo mitosis. As they do, they push preceding generations of cells toward the surface and down the oxygen concentration gradient. Eventually, the keratinocytes occupy a position where they can't get enough oxygen to satisfy their metabolic needs and they die. This process involves degeneration of the nucleus and accumulation of the protein keratin, and is reflected in the layers seen in epidermis.

The epidermis of thick skin presents five distinct layers (Figure 11-3), whereas in thinner skin only three are generally visible. From deep to superficial (which coincides with the stages of development), these are the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. The **stratum basale** is the deepest layer of the epidermis. It is composed of healthy (due to their proximity to the dermal capillaries) cuboidal to low columnar cells that undergo mitosis. The **stratum spinosum** is the thickest layer. It is characterized by the "prickly" appearance of its cells due to the desmosomes that attach adjacent cells. The deeper cells continue mitotic activity, but this ability is lost in the more superficial layers. The **stratum granulosum** is characterized by cells containing dark staining keratohyalin granules, an indication that they have begun to die. It is usually about five cells thick. Secretion of a lipid material by these cells makes the epidermis waterproof. The **stratum lucidum** is characterized by cells that have lost their nuclei and have accumulated keratin. It is only seen in thick skin. The most superficial layer of the

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epidermis is the **stratum corneum**. It consists of dead, anucleate cells that have accumulated abundant keratin. As these cells approach the surface, they lose their intercellular attachments (desmosomes) and are sloughed off.

Besides keratinocytes, other cells are seen in the epidermis. **Langerhans cells** (Figure 11-3c) are a component of the immune system and function as antigen presenting cells. They are characterized by a dark staining nucleus with pale cytoplasm and numerous cytoplasmic extensions (hence their other name, "**dendritic cells**"). They are found in many places, but are most abundant in the stratum spinosum. **Melanocytes** (Figure 11-4) are pale staining cells found in the stratum basale. They produce the brown/black pigment melanin in membrane-bound structures known as melanosomes that are deposited in the cytoplasm of keratinocytes of the stratum spinosum. The melanin accumulates near the nucleus on the side closest to the surface where it protects the nucleus by absorbing ultraviolet radiation. Figure 11-4 shows pigmented skin. **Merkel cells** are found in the stratum basale of fingertips and oral mucosa, and have indented nuclei. They are thought to act as mechanoreceptors.

Dermis

The dermis is deep to the epidermis and is the "true skin." The surface in contact with the epidermis is highly folded into elongated **dermal ridges** or conical **dermal papillae** (Figure 11-5). These interlocking surfaces anchor the epidermis to the dermis and resist separation of the two layers when subjected to shearing forces. Dermal ridges are seen on the surface of the palm and sole as fingerprints.

The portion of the dermis in contact with the epidermis and comprising the dermal papillae is a looser and finer connective tissue and forms the **papillary layer**. The papillae contain capillary loops and tactile receptors called **Meissner's corpuscles** (Figure 11-6). The majority of the dermis is composed of a vascular, dense irregular connective. This is the **reticular layer** (Figure 11-5). Fibroblasts are the most common cell. Large blood vessels, nerves, and epidermal appendages are present in the reticular layer. Pressure receptors called **Pacinian corpuscles** may also be seen (Figure 11-7).

Hypodermis

The hypodermis consists of loose connective tissue and anchors the skin to the underlying tissues without binding it too tightly. This allows free movement of underlying muscles without pulling on the skin. The loose connective tissue may be replaced by fat (Figure 11-8). Hair follicles, Pacinian corpuscles, and sweat glands may be seen.

Appendages of the Skin

The epidermis gives rise to a variety of appendages. These are nails, hair follicles, and sweat glands.

Hair Follicles

The **hair follicle** (Figure 11-9) is an angular downgrowth of the epidermis into the dermis or hypodermis. The base of the follicle is dilated to form the **hair root**, which is penetrated by a **dermal papilla** that houses capillaries. Together, the root and papilla form the **hair bulb**. The follicle is surrounded by a thick basement membrane called the **glassy membrane**, which itself is wrapped in dense connective tissue.

The **hair** is made of keratinized cells. It is produced by dividing cells at the base of the follicle called the **hair matrix**, which is the functional equivalent of the stratum basale of the epidermis. Thus, the hair grows from its base, not its tip. Cells become keratinized in a mechanism similar to that seen in the epidermis. The portion of the hair above the skin's surface is called the **hair shaft**. Frequently, the hair falls out of the follicle during slide preparation, so all that is seen is the follicle and associated structures.

Two types of hairs are present in humans. **Vellus hairs** are short, fine, and microscopic. These comprise the majority of hairs on the human body. **Terminal hairs** are larger and coarser. These are the hairs everyone recognizes as hairs.

In cross section, the hair and follicle present several layers (Figure 11-10).

- The **medulla** is at the center of the hair. It is most obvious in the root; in the shaft the cells are cornified or completely absent.
- The **cortex** makes up the bulk of the hair. In the root, the cortex is made of cuboidal cells, but in the shaft the cells are flattened and keratinized. Pigment granules and air spaces between the cortical cells produce hair color.
- The **cuticle** of the hair is made of hard keratin and surrounds the cortex.
- The **internal root sheath** extends from the base of the follicle to where the sebaceous gland enters. It consists of three layers. The **cuticle of the internal root sheath** is similar in construction to the cuticle of the hair and its cells interdigitate with it. **Huxley's layer** consists of a couple of layers of flattened cells. **Henle's layer** is a single row of flattened rectangular cells.
- The **external root sheath** is composed of several cell layers. The single layer of cells in contact with the connective tissue sheath is columnar; the remaining cells are polygonal in shape. These cells are derived from the outermost part of the matrix and are separated from the connective tissue sheath by the glassy membrane.

Sebaceous Glands

Hair follicles are associated with branched acinar **sebaceous glands** (Figures 11-9a and 11-11). Gland cells near the follicle disintegrate and release the oily substance sebum into

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the follicle, which moisturizes and lubricates the hair. Division of cells at the base of the gland replaces these cells. Because sebaceous glands are thicker than their respective follicle, these glands are often seen in specimens without their follicle.

Arrector Pili Muscles

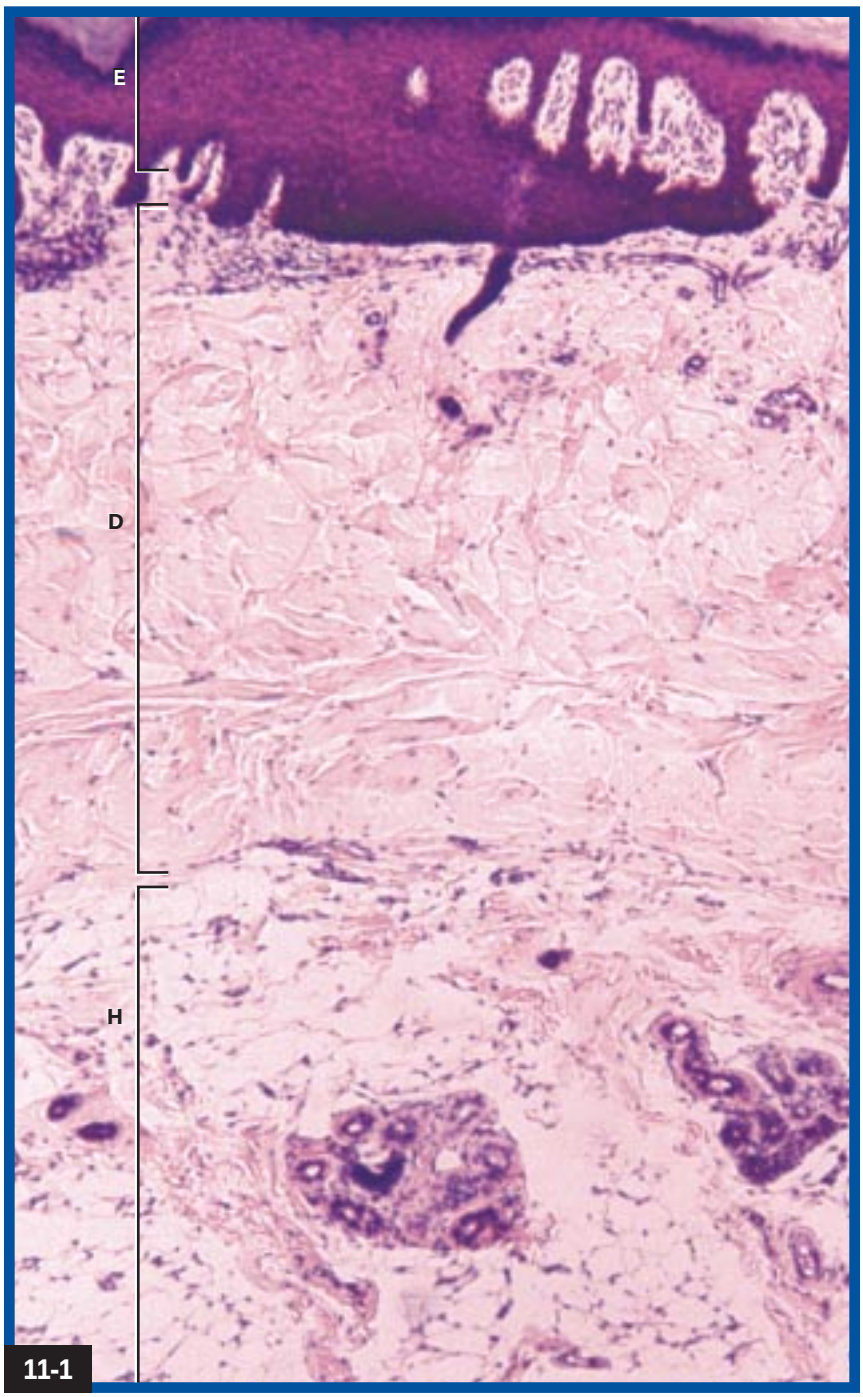
Arrector pili muscles (Figures 11-9a and 11-12) are smooth muscles that insert on the follicle's connective tissue sheath. They are positioned in the obtuse angle formed by the follicle and the skin surface. Their contraction straightens the hair, which in other mammals causes the fur to form a thicker insulating layer, but in humans only produces "goose bumps." The sebaceous gland is found in the angle formed between the arrector pili and the follicle.

Sudoriferous (Sweat) Glands

Sudoriferous or **sweat glands** are downgrowths of the epidermis. They are simple, coiled tubular glands of two types. **Merocrine sweat glands** (Figures 11-13a and 11-13b) are more numerous and produce a watery secretion as a stress response or a cooling response. The coiled secretory portion is made of simple cuboidal epithelium and the lumen is small. The relatively straight duct leading to the surface is made of two cell layers. **Apocrine sweat glands** (Figure 11-13d) are found in the axillary and groin regions. The lumen of the secretory portion is wider than in merocrine glands and the secretion is more viscous.

Nails

Nails (Figure 11-14) are made of keratinized cells that form a hard plate on the dorsal and distal sides of the fingers and toes. The main part of the nail is the **nail plate** that ends distally as the **free edge**, the part that gets trimmed. At the proximal end is the **nail root** that lies beneath a fold of skin. The nail rests on an epidermal layer (corresponding to the stratum basale and stratum spinosum) called the **nail bed**. At the proximal end, the nail bed is thickened to form the **nail matrix**. It is responsible for producing the nail in a process similar to hair production. The stratum corneum folds over the proximal end of the nail plate as the **eponychium** and under the free edge as **hyponychium**.



THE INTEGUMENT The integument consists of the superficial epidermis (E), a keratinized stratified squamous epithelium, and the deeper dermis (D), a dense irregular connective tissue. The hypodermis (H) is deep to the dermis and is adipose tissue in this specimen. *(X65)*

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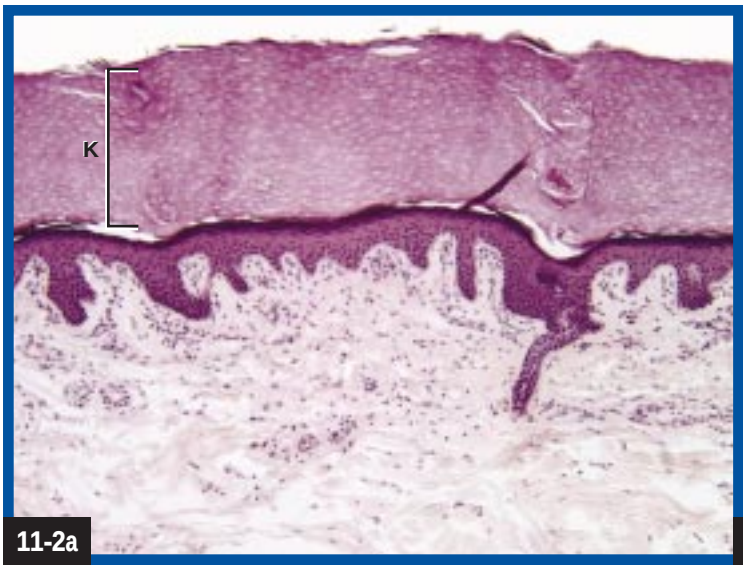
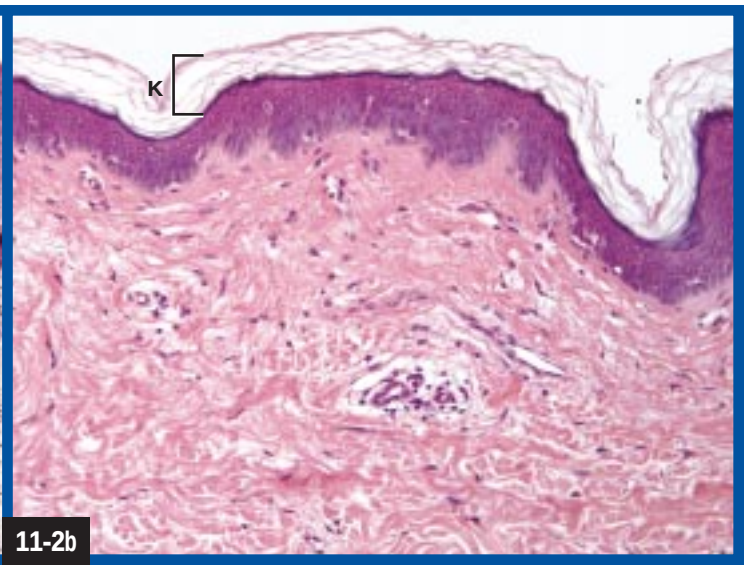
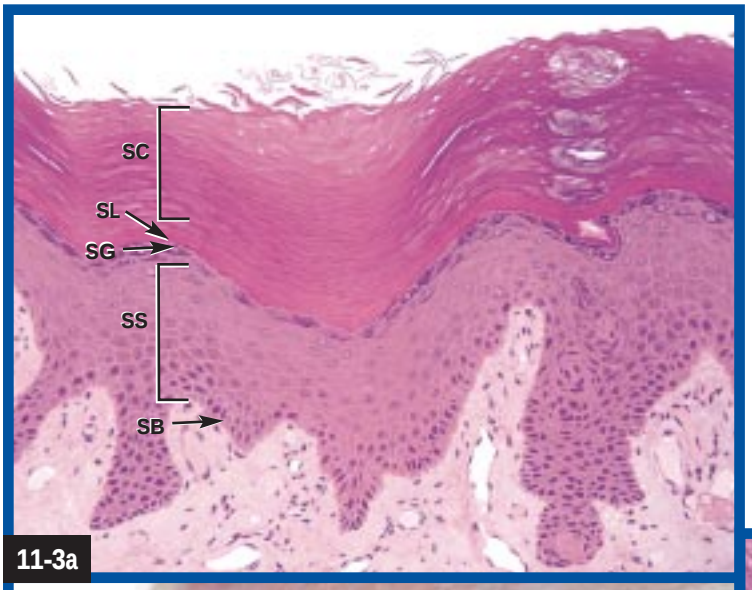
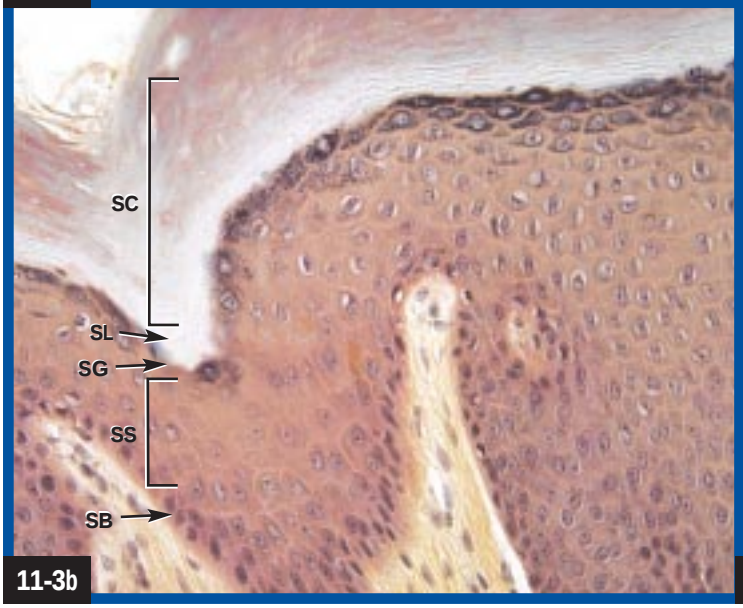


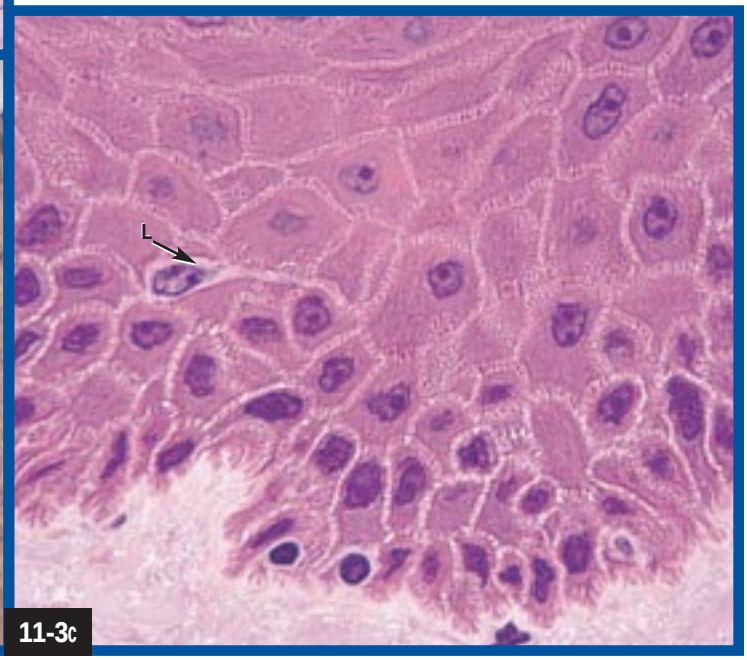


THICK AND THIN SKIN (a) This specimen is from the sole of the foot and is representative of thick skin. Note the thick keratinized layer (K) on the surface. *(X65)* (b) Thin skin has a much thinner keratinized layer that appears shredded. *(X130)*





EPIDERMAL LAYERS The epidermis of thick skin presents five layers, each representing a stage in the life of a keratinocyte. From deep to superficial, these are the stratum basale (SB), stratum spinosum (SS), stratum granulosum (SG), stratum lucidum (SL), and stratum corneum (SC). (a) *X130* (b) *X265* (c) The stratum spinosum is characterized by cells with spiny intercellular junctions. Note the Langerhans (dendritic) cell (L). *(X660)*



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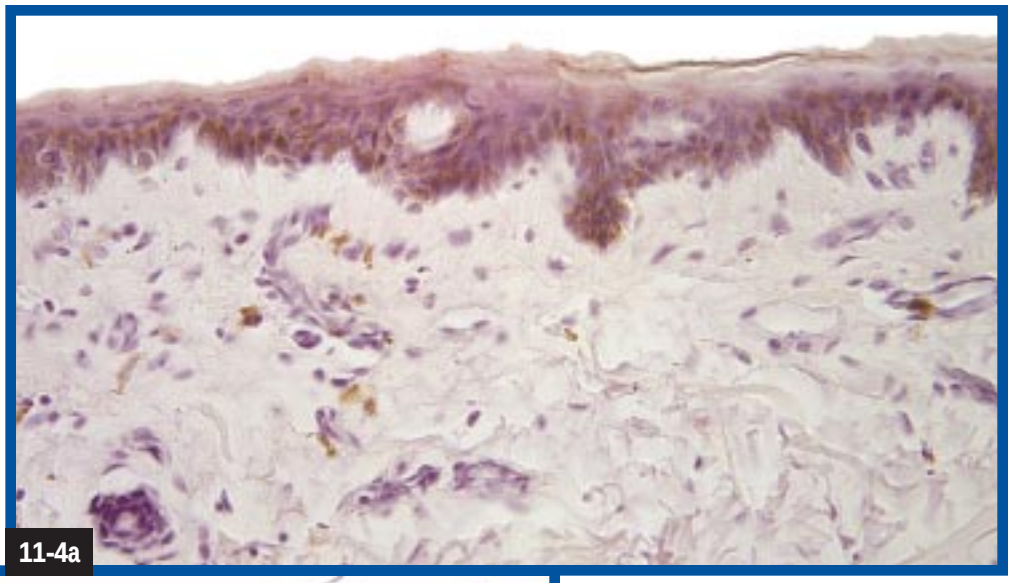

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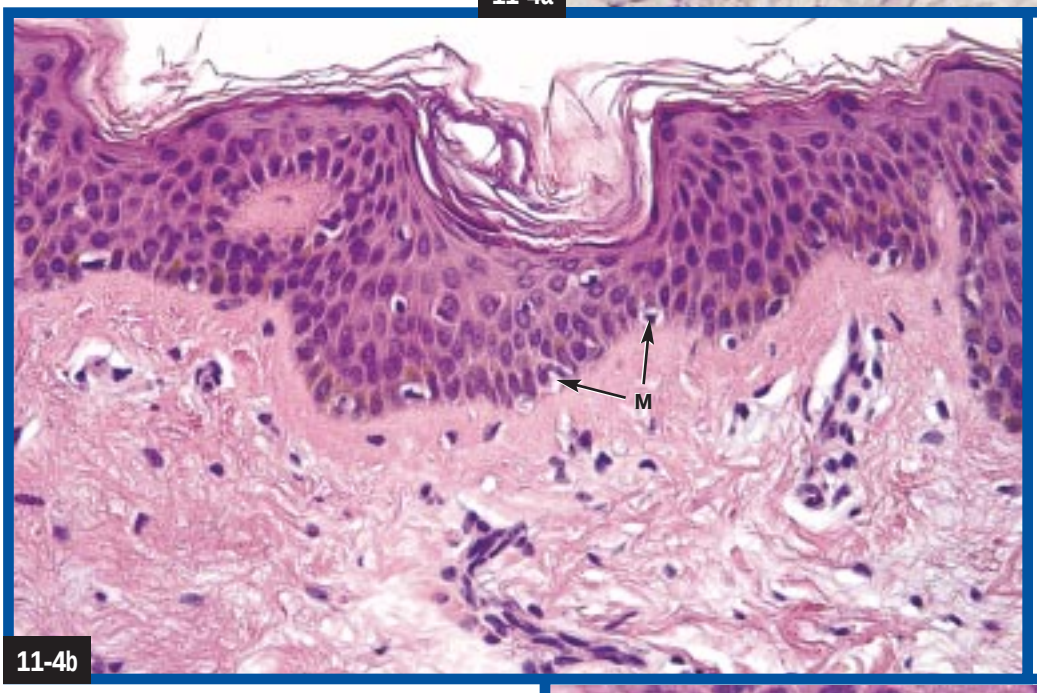

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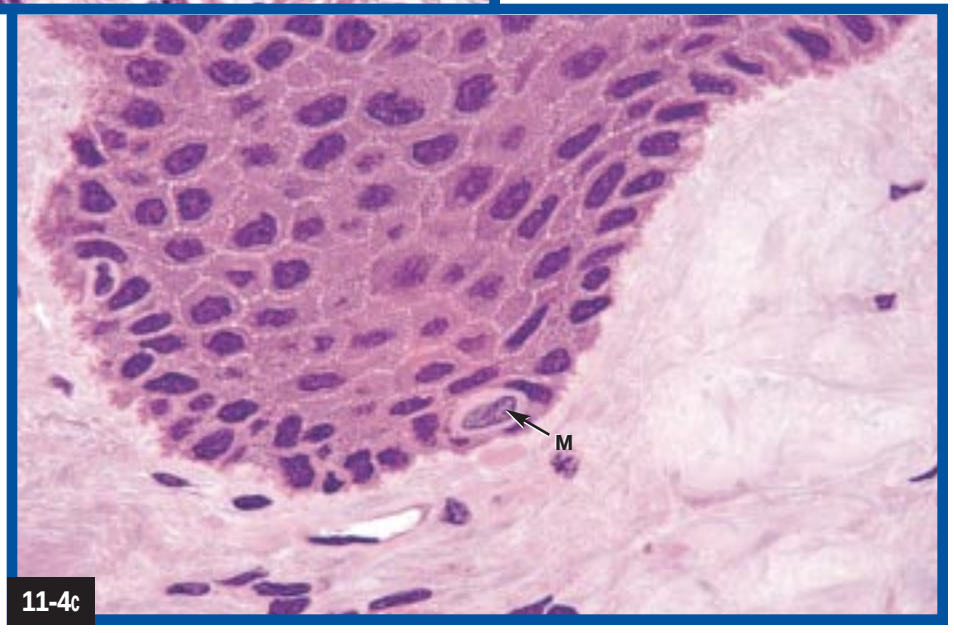

11-4c

PIGMENTED SKIN Skin accumulates a brown to black pigment called melanin. This pigment accounts for the color of darker skinned races, and the tanning in lighter skinned races. (a) This is pigmented thin skin. Note the abundance of melanin in the basal layers of the epidermis. *(X265)* (b) This thin skin specimen is pigmented, but not as much as (a). Note the melanocytes (M). *(X265)* (c) Melanin is produced by melanocytes. These are large, pale staining cells found in the basal layers of the epidermis. Also note the spiny cells of the stratum spinosum. *(X660)*

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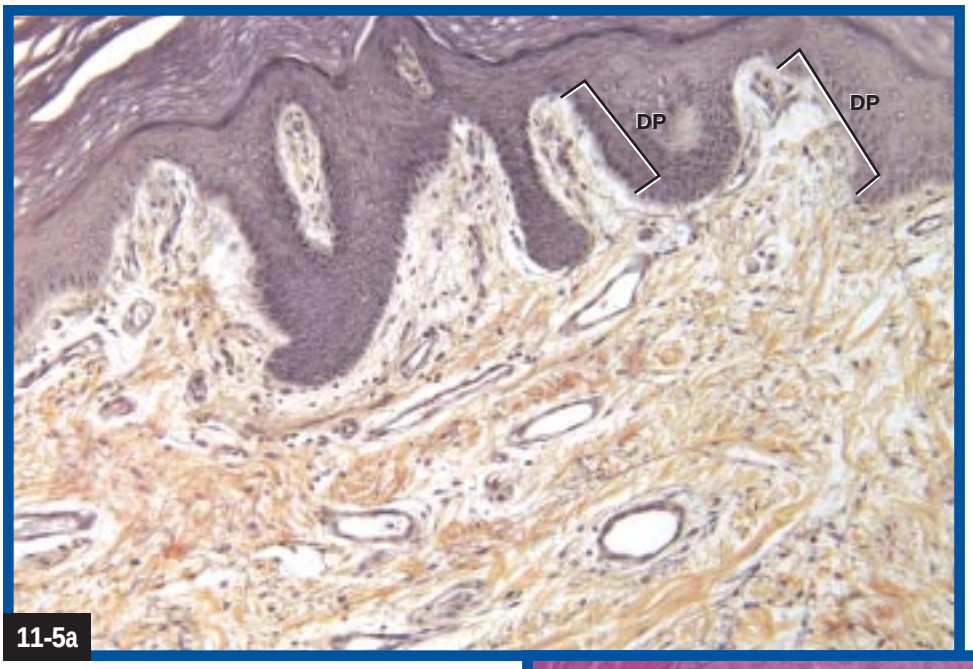
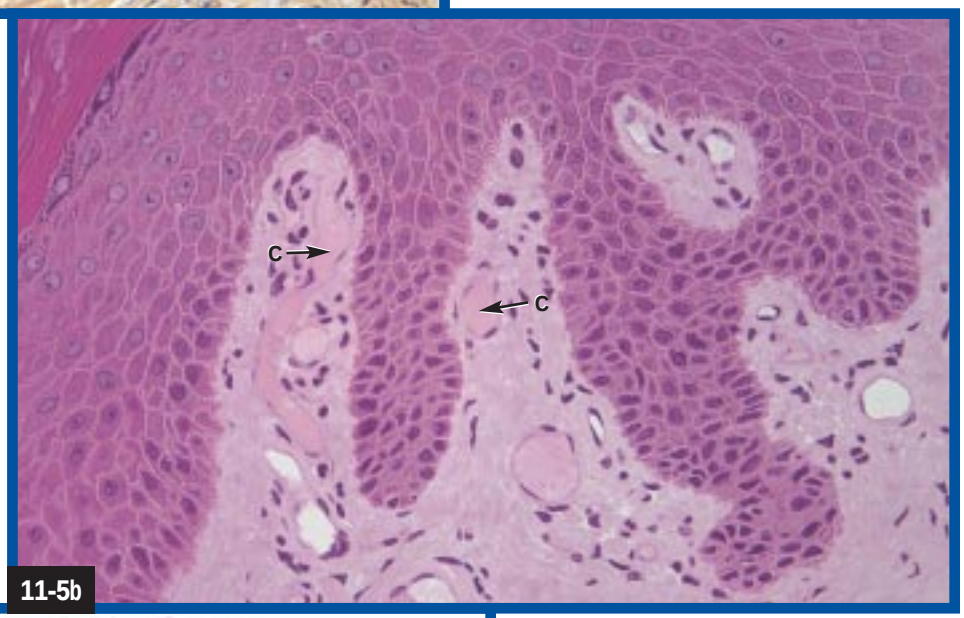


11-5a

DERMIS (a) Dermal papillae (DP) project into the epidermis. The irregular margin between the two layers increases surface area and limits separation due to shearing forces. *(X130)* (b) This micrograph shows capillaries (C) in the dermal papillae. *(X260)* (c) The papillary layer (P) of the dermis is in contact with the epidermis and is made of a loose connective tissue. The deeper reticular layer (R) is thicker and much coarser. The difference in texture is obvious in this micrograph. *(X130)*



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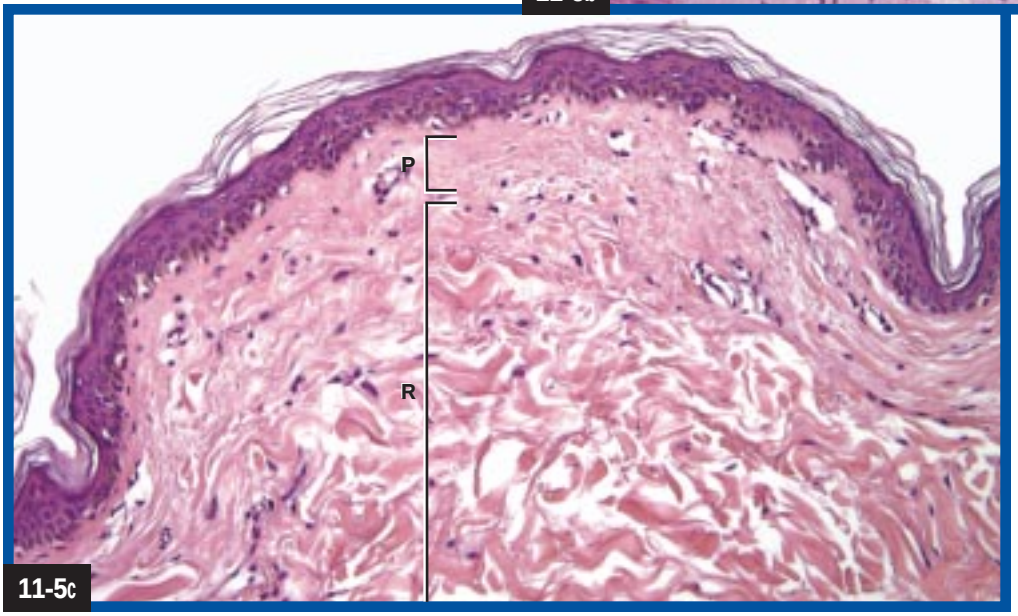

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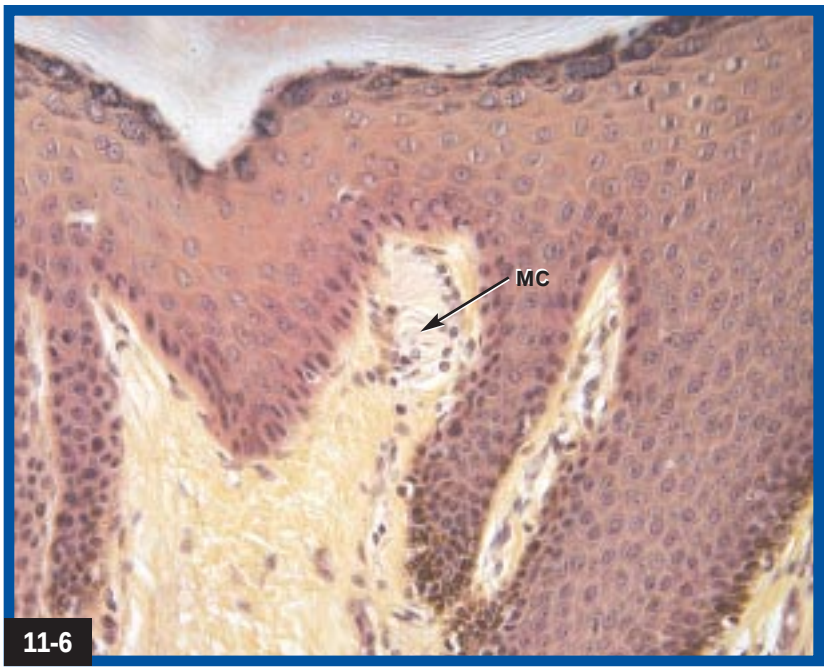
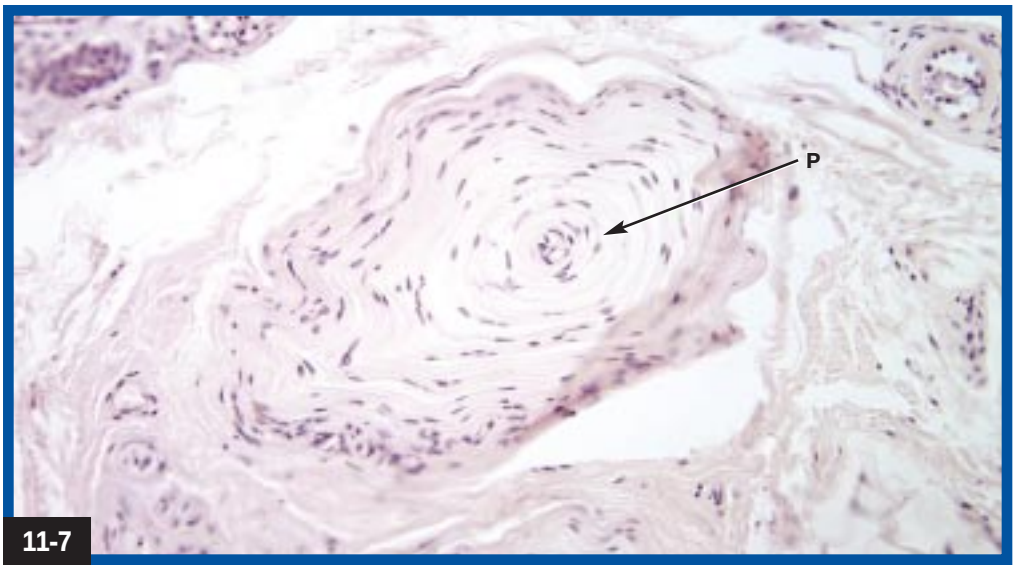
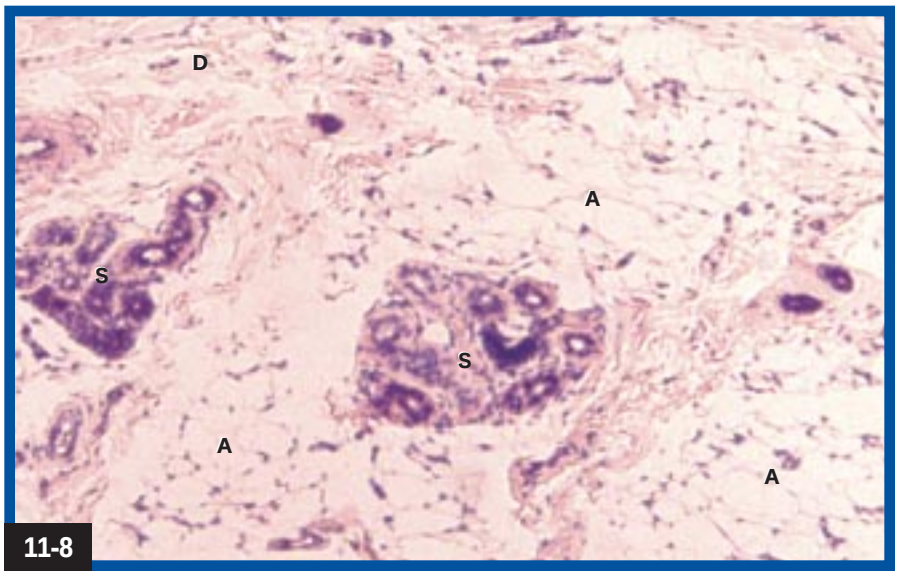


MEISSNER'S CORPUSCLES Meissner's corpuscles (MC) are receptors for light touch found in dermal papillae. *(X210)*



PACINIAN CORPUSCLES These pressure receptors (P) look like a sliced onion in section and are found in the dermis and hypodermis. *(X130)*



HYPODERMIS Deep to the dermis (D) is a layer of loose connective tissue or adipose tissue (A) that loosely binds the integument to the underlying structures. It allows free movement of muscles without pulling on the skin. This micrograph shows adipose tissue and two sweat glands (S) in the hypodermis. *(X130)*

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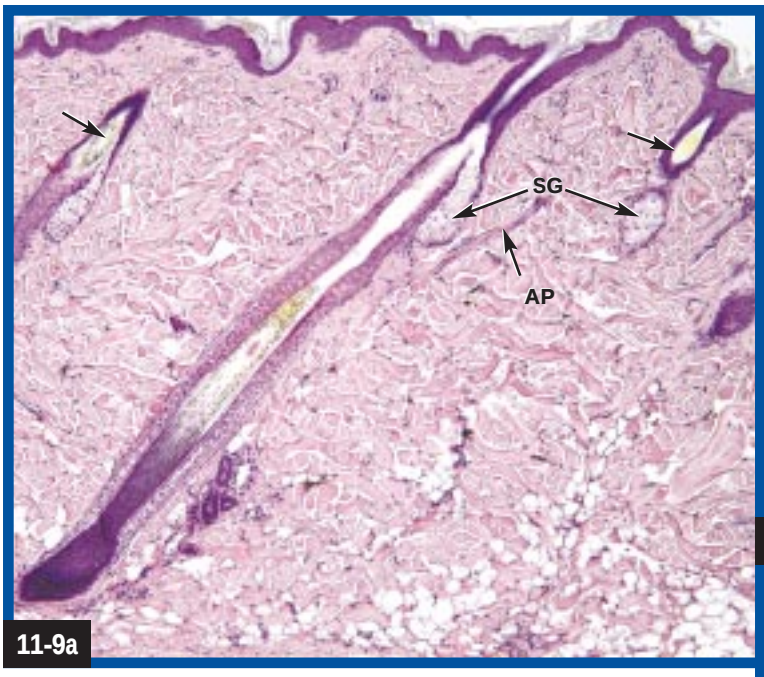
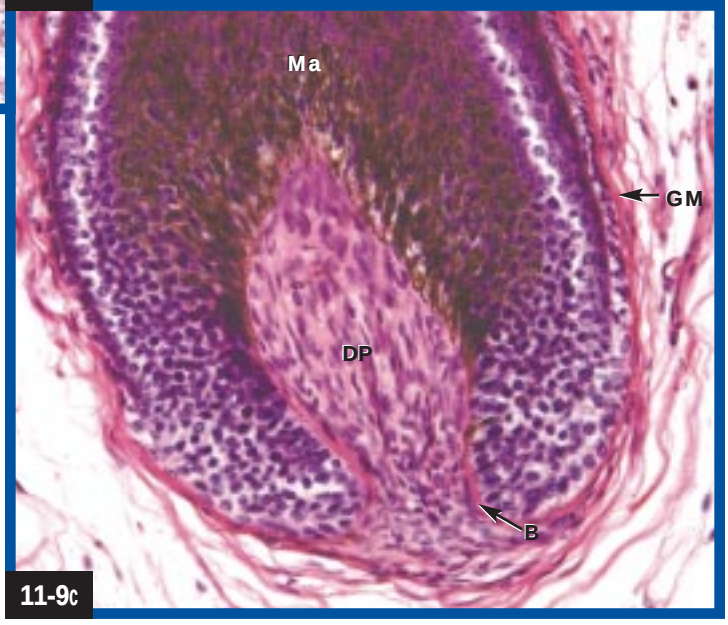
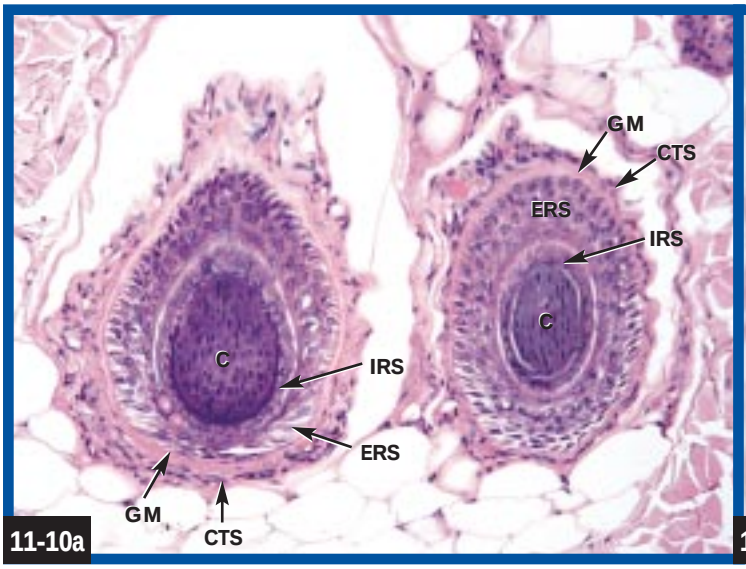




HAIR FOLLICLE Hair follicles are epidermal invaginations into the dermis. They form an angle with the surface and rarely are seen in their entirety due to the sections being so thin. (a) This shows a fairly complete hair follicle, but pieces of other follicles are also visible (arrows). Sebaceous glands (SG) and an arrector pili muscle (AP) can also be seen. *(X50)* (b) The deepest part of the follicle is dilated and forms the hair bulb (HB). Also visible are the cortex (C), and external root sheath (ERS). *(X110)* (c) Each follicle has a dermal papilla (DP) that has a capillary and a nerve. It is separated from the hair root cells by a basement membrane (B), which is continuous with the glassy membrane (GM) on the outside of the follicle. Note the large amount of pigment in the hair matrix cells (Ma). *(X400)*



HAIRS IN CROSS SECTION (a) This cross section of two hair follicles was made at the level of the hypodermis. Key to the symbols used: **C** = cortex, **Cu** = cuticle, **IRS** = internal root sheath, **ERS** = external root sheath, **GM** = glassy membrane, **CTS** = connective tissue sheath. *(X130)* (b) This section was made higher in the dermis. Symbols used are the same as in (a). *(X260)*

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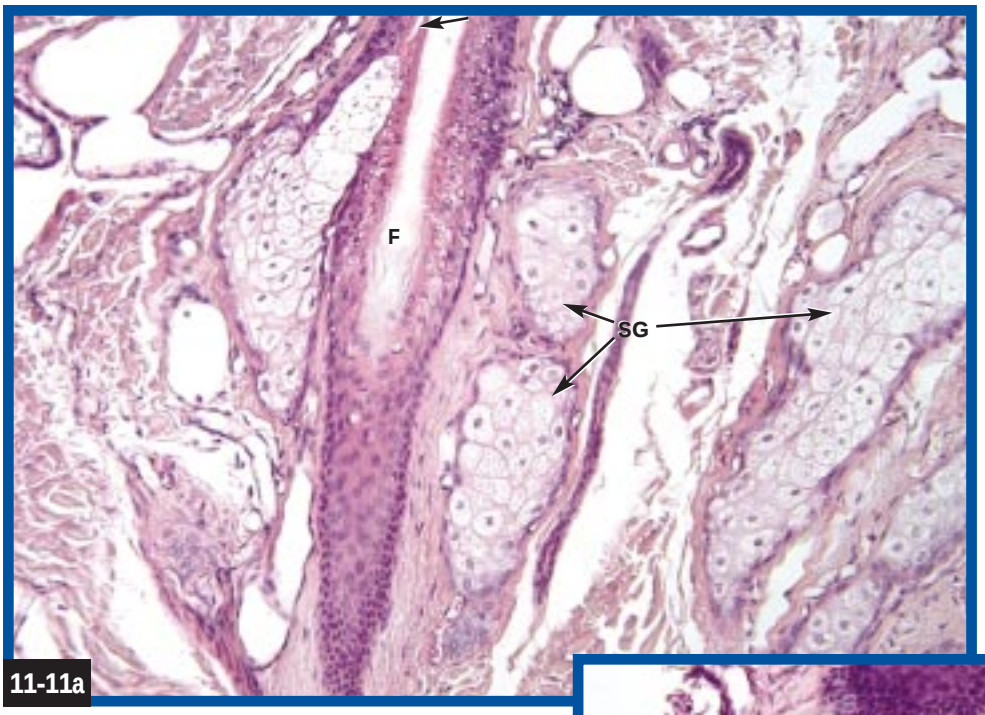

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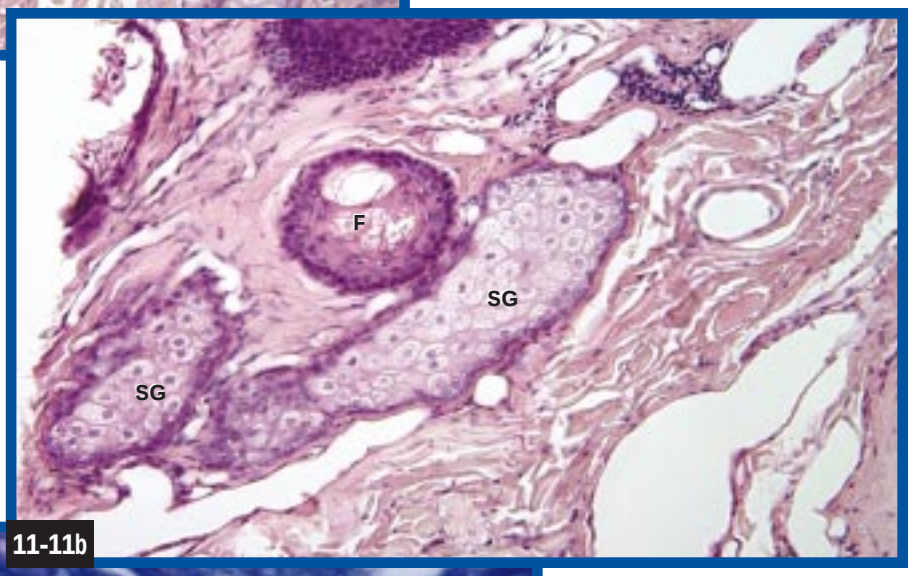

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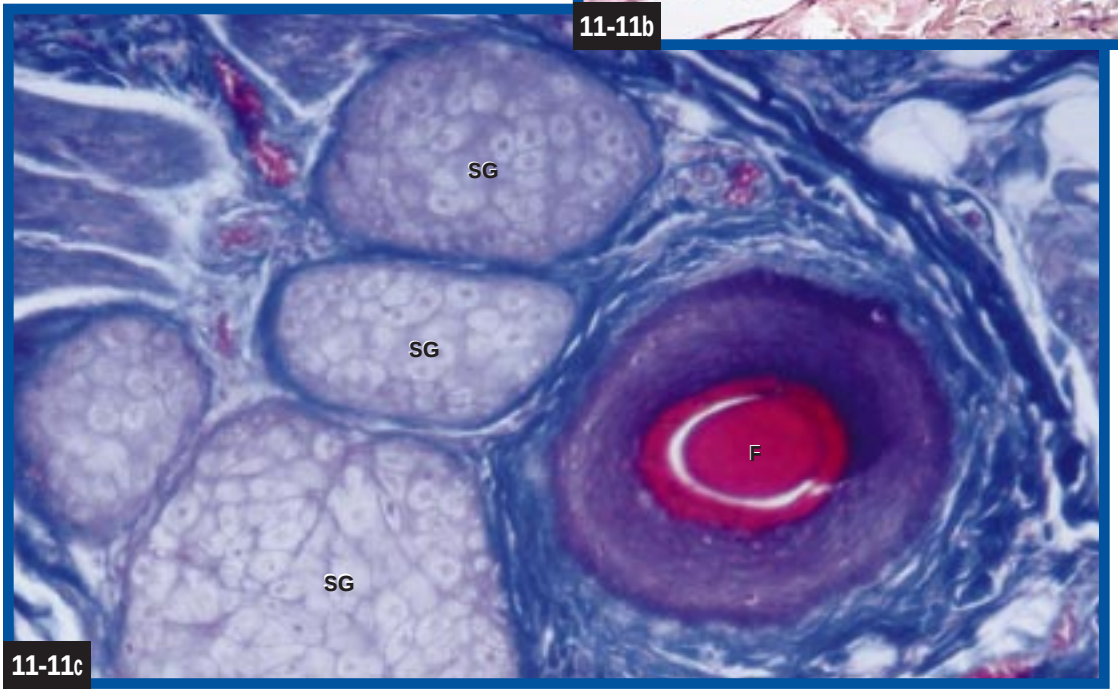

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SEBACEOUS GLANDS Cells of sebaceous glands (SG) are large and often have a foamy appearance. Because they are larger than their associated follicle (F), sebaceous glands are often seen with no follicle in the section. (a) The sebaceous gland on the left is seen to empty into the follicle (arrow). The ducts of the others are out of the plane of section. *(X130)* (b) Shown here is a follicle cut in oblique section. The sebaceous glands show no connection with it. *(X130)* (c) In this cross section, the size of sebaceous glands relative to their follicle is seen. *(X250)*

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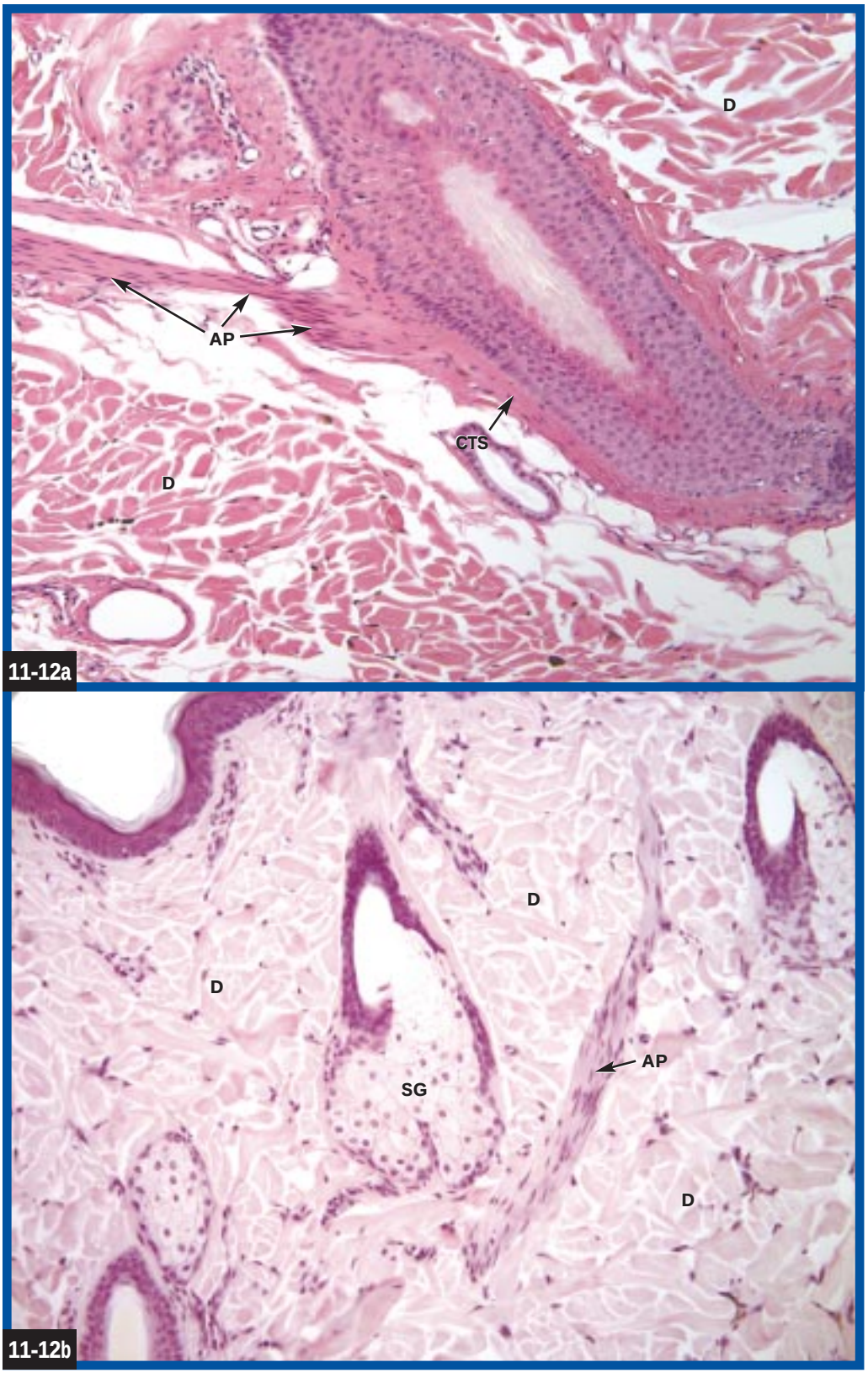

ARRECTOR PILI MUSCLES Contraction of an arrector pili muscle causes the hair to straighten. (a) This micrograph shows an arrector pili (AP) muscle attachment to the connective tissue sheath (CTS) of a follicle cut in oblique section through the dermis (D). *(X130)* (b) It is very difficult to find a perfectly sectioned hair follicle, so one has to make do with what is available. In this micrograph, no follicle is present, but the sebaceous gland (SG) and arrector pili muscle are seen in the dermis. *(X130)*

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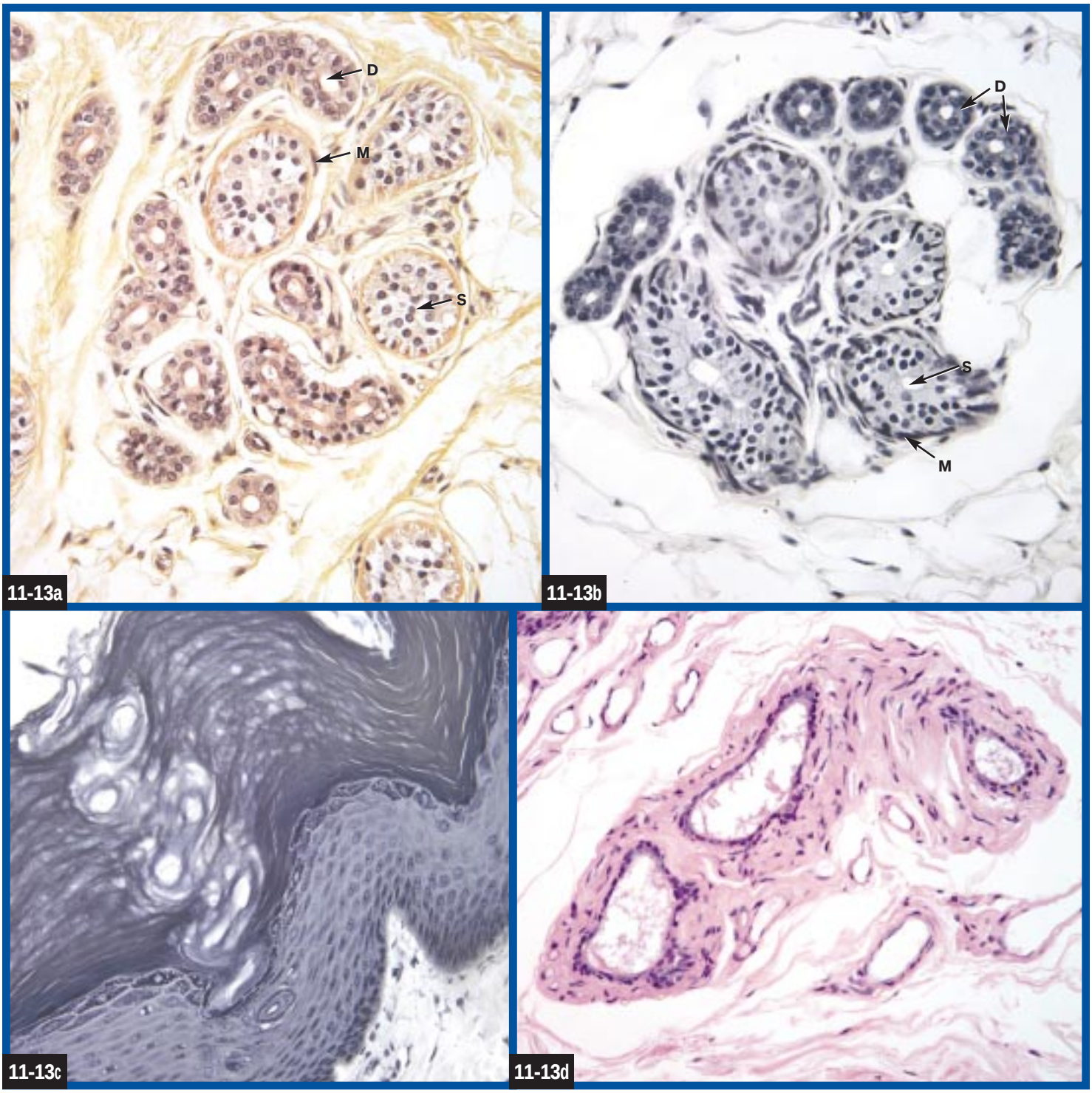

SWEAT GLANDS Sweat glands are of two types—merocrine and apocrine. (a and b) Here are two merocrine sweat glands in the hypodermis. The secretory portion (S) is highly coiled, has large pale staining cells, and a small lumen. Myoepithelial cells (M) are associated with the secretory portion. The duct (D) is lined with two layers of darker staining cells. (*X260*) (c) This micrograph shows a sweat gland duct as it passes through the stratum corneum. (*X210*) (d) Apocrine sweat glands are found in the axillary and genital regions. The secretory portion is coiled and tubular with a large lumen. The ducts empty into hair follicles and are similar in construction to the ducts of merocrine sweat glands. *(X210)*

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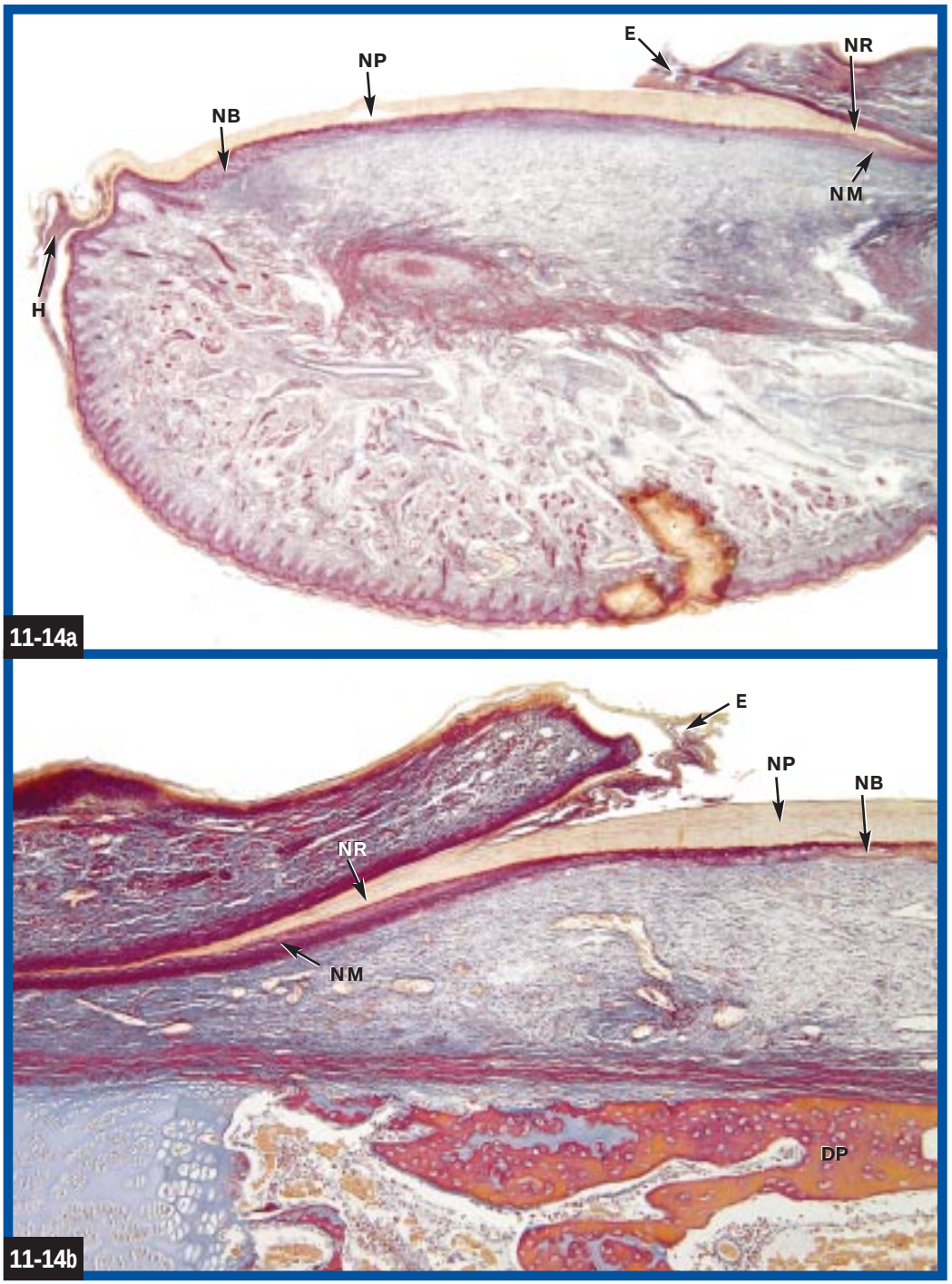

NAILS (a) This micrograph is of a fetal finger cut in sagittal section. Notice the continuity of the stratum corneum with the eponychium and hyponychium. (*X25*) (b) This micrograph shows greater detail of the nail root. (*X65*) Key to symbols used: **NB** = nail bed, **NM** = nail matrix, **NP** = nail plate, **NR** = nail root, **E** = eponychium, **H** = hyponychium, and **DP** = distal phalanx.

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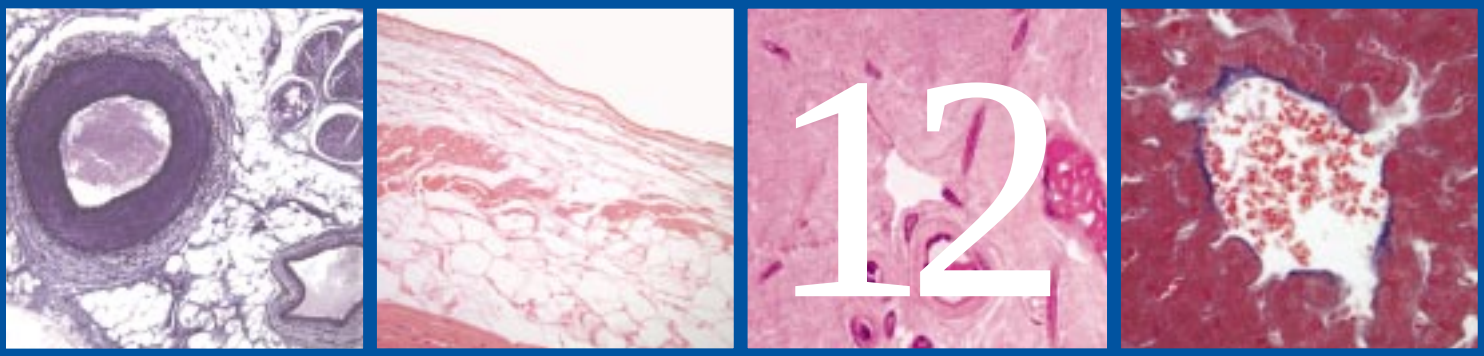
Cardiovascular System

CHAPTER 12



Introduction to the Cardiovascular System

The cardiovascular system consists of blood pumped by the heart through the blood vessels to all parts of the body. Its function is to carry materials from organs that exchange with the environment to and from cells buried deep in the body. Oxygen is picked up in the lungs and distributed throughout the body, whereas carbon dioxide is picked up from the cells and delivered to the lungs where it is exhaled. Food absorbed by the digestive tract is distributed throughout the body, and wastes are picked up from cells and removed from the blood by the kidneys.

The human circulatory system consists of two closed-loop paths: the **pulmonary circuit** and the **systemic circuit**. In the adult, oxygen-poor blood is returned to the right atrium by the superior and inferior venae cavae. From here, it moves to the right ventricle and is pumped out into the pulmonary trunk where it is then sent to the lungs to pick up oxygen. It is returned to the left atrium by the pulmonary veins. This completes the pulmonary circuit. From the left atrium, the now oxygen-rich blood is sent to the left ventricle and is then pumped out the aorta to be distributed to the capillaries of the entire body. Blood in the capillaries loses its oxygen to the surrounding tissues, picks up CO_2 and is sent back to the right atrium. This completes the systemic circuit.

Basic Blood Vessel Structure

Blood vessels are composed of as many as three layers or tunics that are modified according to the vessel's function. From innermost tunic to outermost these are the tunica (intima) interna, tunica media, and tunica (adventitia) externa. They are best demonstrated in arteries (Figure 12-1).

The **tunica interna** is a simple squamous endothelium supported by a thin layer of connective tissue. In some vessels (arteries), an **internal elastic (lamina) membrane** is also present at the junction with the tunica media. The **tunica media** is composed of varying amounts of smooth muscle and elastic connective tissue oriented circularly around the vessel. In larger arteries, there may be an **external elastic lamina** or **membrane** at the junction with the tunica externa. The tunica externa is composed of fibrous connective tissue that often blends with surrounding connective tissues, making the outer limit of the vessel difficult to see.

If the vessel's walls are thicker than the effective distance for diffusion of oxygen and nutrients, the wall may be penetrated with small blood vessels called **vasa vasorum**. They are especially common in larger veins due to the lower oxygen concentration in systemic venous blood.

Types of Blood Vessels

Blood vessels are of three main types: arteries, veins, and capillaries. Each has a distinctive structure appropriate to its function. Arteries, veins, and nerves typically travel together to form a **neurovascular bundle** (Figure 12-2).

Arteries carry blood away from the heart at high pressure. As such, their walls are thicker than their corresponding vein. The two arteries that exit the heart are the aorta and pulmonary trunk. These branch into smaller and smaller arteries and eventually lead to the capillaries of the systemic circuit and pulmonary circuit, respectively. As arteries get

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smaller, the proportion of elastic tissue decreases and the smooth muscle increases (relative to the wall's thickness). As viewed under the microscope, arteries typically have a circular lumen, distinct layers, and the tunica media is the thickest of the three (Figure 12-3).

Elastic arteries (Figure 12-3) are the largest and include the pulmonary trunk and aorta, and their major branches. The tunica media is dominated by elastic tissue in the form of fenestrated membranes, which alternate with smooth muscle. Internal and external elastic membranes are present. The tunica adventitia is very thin and often has vasa vasorum.

Muscular arteries (Figure 12-4) are larger than 0.5 mm in diameter and include most of the named arteries. The internal elastic membrane is wavy in appearance and the tunica media is composed of up to 40 layers of smooth muscle cells. An external elastic membrane may be present and the tunica adventitia has collagen, and elastic and smooth muscle fibers oriented longitudinally along the vessel.

Arterioles (Figure 12-5) are the smallest arteries, with a diameter of 30 to 200 µm. The tunica media is composed of one to a few layers of smooth muscle. An internal elastic membrane is present in larger arterioles but is absent in smaller ones. The tunica adventitia is approximately the same size as the tunica media. The final arteriole before the capillary bed is called a **metarteriole**. Blood flow into the capillary bed is regulated by **precapillary sphincters**, circularly arranged smooth muscle fibers around the capillaries emerging from the metarteriole. An **arteriovenous anastomosis** directly connects the arteriole and venule and allows blood to bypass the capillary bed when the sphincters are closed.

Capillaries are the smallest blood vessels. The have a diameter of 4 to 10 µm and consist only of endothelium and basal lamina. Contractile **pericytes** may be present on capillaries (and some venules). They regulate blood flow.

Based on electron micrographs, three types of capillaries are recognized (Figure 12-6). **Continuous capillaries** have a complete endothelial lining. They are the most common and are found in muscle, nervous, and connective tissues, as well as the lungs. In **fenestrated capillaries**, membrane-covered pores 60 to 80 nm in diameter are present. These are found in endocrine glands, lamina propria of the small intestine, and kidneys (where there is no membrane covering the pores). **Sinusoidal capillaries** are larger than other capillaries and the surrounding cells determine their shape. Their discontinuous endothelium promotes exchange. They are found in bone marrow, the liver, spleen and lymph nodes, as well as other places.

Veins carry blood toward the heart under low pressure. Their walls are thinner than the corresponding artery. Veins begin at the capillaries and end at the heart as either the inferior or superior vena cava or the pulmonary veins. Because they carry blood at low pressure and against the pull of gravity, many veins are supplied with endothelial folds that form **valves**. As viewed under the microscope, veins often are collapsed and have an irregularly shaped lumen, the layers are indistinct and the thickest layer is the tunica externa (compare with the artery in Figure 12-2).

The smallest veins are called **venules** (Figure 12-5). Venules are structurally similar to capillaries, but are larger in diameter. As they emerge from the capillary bed, pericytes are present, but these are replaced with smooth muscle in the tunica media as the venules get larger. **High endothelial venules** are found in certain lymphatic organs and have a cuboidal endothelium.

Medium veins are less than 1 cm in diameter (Figure 12-7). Their tunica intima is composed of endothelium and connective tissue, but there is no internal elastic membrane. The tunica media consists of smooth muscle, and the tunica adventitia has collagen and elastic fibers, and smooth muscle. Valves formed by pockets of tunica intima are present in medium veins that carry blood against gravity (Figure 12-8). If blood flows the wrong way, the pockets fill with blood and the lumen is closed.

Large veins (Figure 12-9) have a thicker tunica intima due to more connective tissue. The tunica media is generally absent, though smooth muscle cells are present in veins carrying blood against gravity. The tunica adventitia is the thickest layer and is composed of elastic and collagen fibers. Vasa vasorum are also present.

The Heart

The heart is a hollow, muscular organ. It consists of four chambers: the **right atrium** and **ventricle**, and the **left atrium** and **ventricle**. The superior vena cava brings blood from the head and upper limbs to the right atrium, whereas the inferior vena cava does the same for the lower limbs and abdomen. The pulmonary trunk emerges from the right ventricle. Pulmonary veins bring blood from the lungs to the left atrium and the aorta carries blood out of the left ventricle.

Valves in the heart ensure blood travels in the correct direction. Between each atrium and its ventricle is an **atrioventricular valve**. The **tricuspid valve** is between the right atrium and ventricle and consists of three flaps. The **bicuspid (mitral) valve** has two flaps and separates the left atrium and ventricle. At the base of the aorta and pulmonary trunk is a **semilunar valve** made of endothelial pockets similar in construction to the valves of veins. These valves prevent backflow into the ventricle during ventricular relaxation (diastole).

The heart wall consists of three layers. The **endocardium** is comparable to the tunica intima of blood vessels (Figure 12-10). It consists of endothelium plus a loose connective tissue. The endocardium folds inward and is reinforced with

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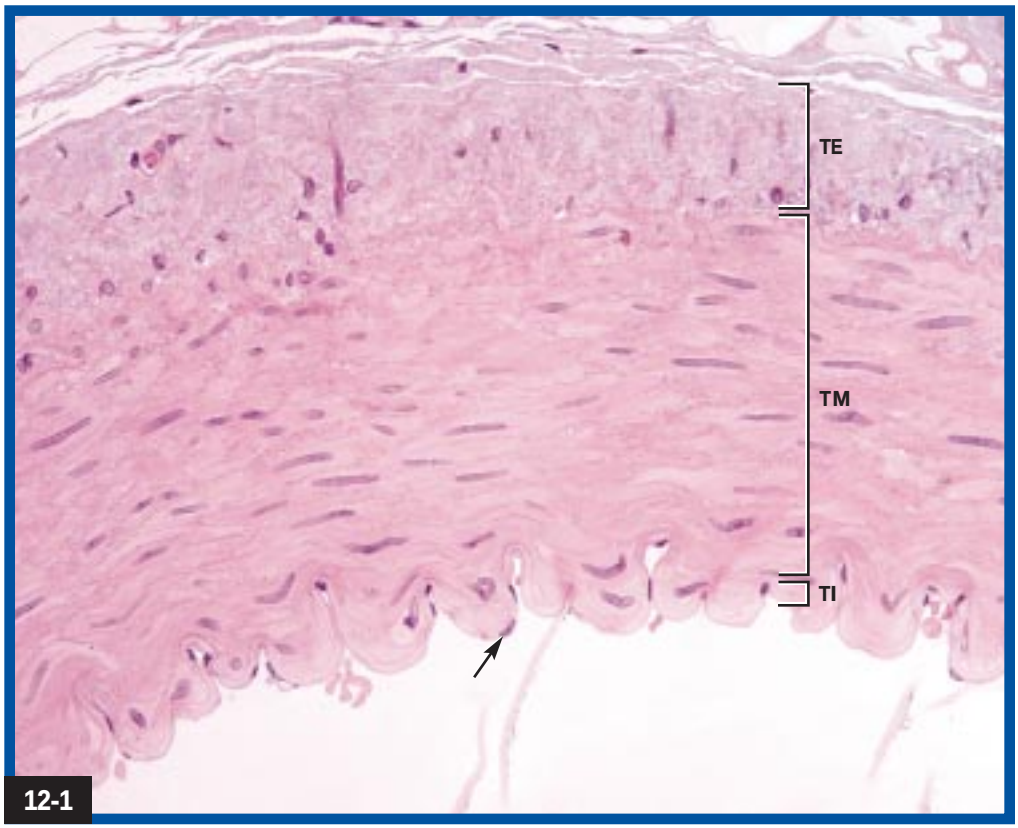
connective tissue to form the flaps of the bicuspid and tricuspid valves. The **myocardium** (Figure 12-11) is the middle and thickest layer of the heart wall. It is composed of cardiac muscle and is highly vascular. Specialized cardiac muscle fibers called **Purkinje fibers** are found in the subendocardial region. Purkinje fibers are part of the heart's conducting system (see below) and transmit impulses from the **atrioventricular node** to the apex of the heart. **Epicardium** is on the outer surface of the heart (Figure 12-12). It is also called **visceral pericardium** and is made of a simple squamous mesothelium plus underlying fibrous connective tissue, which sometimes accumulates fat. It also is the layer in which the **coronary vessels** travel.

Cardiac muscle cells have an intrinsic contraction rate, but the **sinoatrial (SA) node**, located at the junction of the superior vena cava and the right atrium, regulates that rate. The SA node and the following structures constitute the conduction system of the heart. The SA node's signal spreads over the atria causing their contraction. It also reaches the **atrioventricular (AV) node** located in the myocardium near the tricuspid valve. When stimulated, the AV node sends its own signal via the **bundle of His** down the interventricular septum to the heart's apex. From there, the signal spreads upwards through the ventricular myocardium along specialized cardiac muscle fibers called Purkinje fibers, causing contraction (Figure 12-13). Purkinje fibers are located deep to the endocardium and are distinctive due to their large size, lack of striations and pale cytoplasm. They are sometimes binucleate.

The **cardiac skeleton** is made of dense connective tissue. It separates the atria from the ventricles and is also found at the bases of the pulmonary trunk and aorta. It is an attachment site for cardiac muscle and prevents transmission of impulses from the atria to the ventricles except via the bundle of His.



BLOOD VESSEL STRUCTURE The innermost layer in a blood vessel, the tunica interna (TI), is composed of a simple squamous endothelium (arrow) and underlying connective tissue. It is the only layer found in all blood vessels. Depending on the vessel, the tunica media (TM) is made of fibrous and/or elastic connective tissue and smooth muscle. It is absent in capillaries. The tunica externa (TE) is on the outside of vessels other than capillaries. *(X250)*

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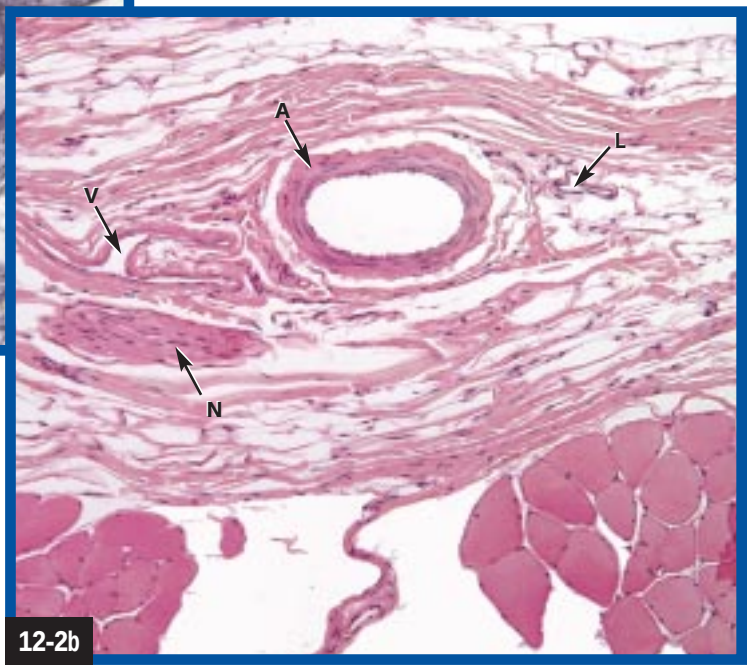
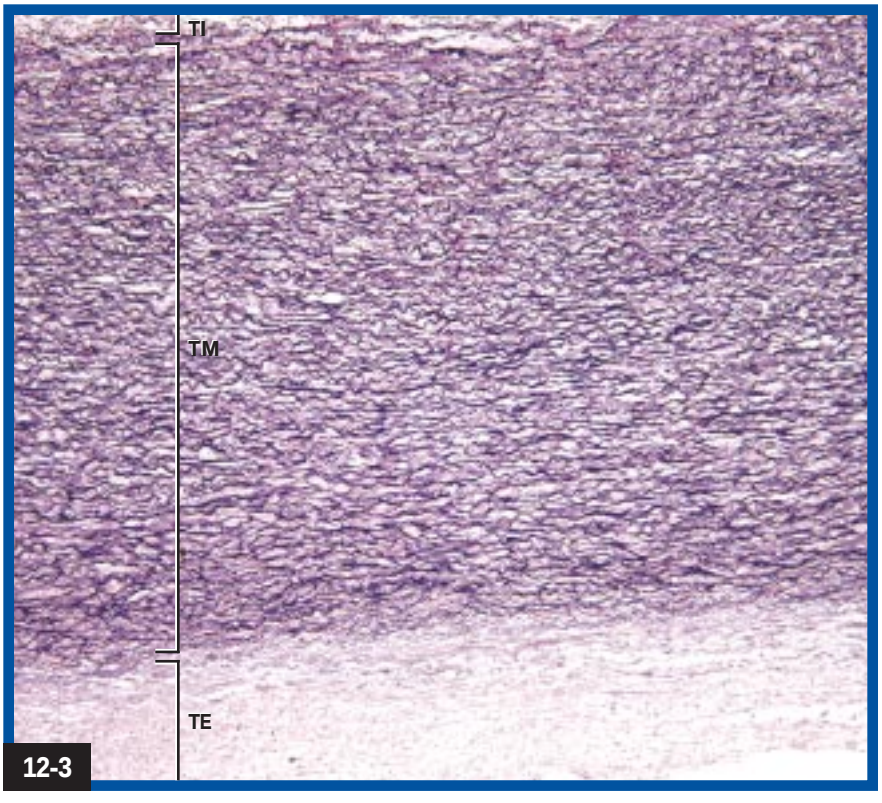
12-2a



12-2b

NEUROVASCULAR BUNDLE Typically arteries (A), veins (V), and nerves (N) are found together in the body. Collectively, they are known as a neurovascular bundle. (a) Shown in this micrograph is a fairly large neurovascular bundle. Notice the round lumen and thicker wall layers in the artery. Corresponding layers in the walls of the artery and vein stain the same. (*X60*) (b) This is a much smaller neurovascular bundle and includes a small lymph vessel (L). *(X120)*



12-3

AORTA In this specimen of the aorta, the fenestrated elastic membranes are visible in the tunica media (TM) as black lines. They account for the elasticity of this large artery. The tunica externa (TE) and part of the tunica interna (TI) are also visible. *(X65)*

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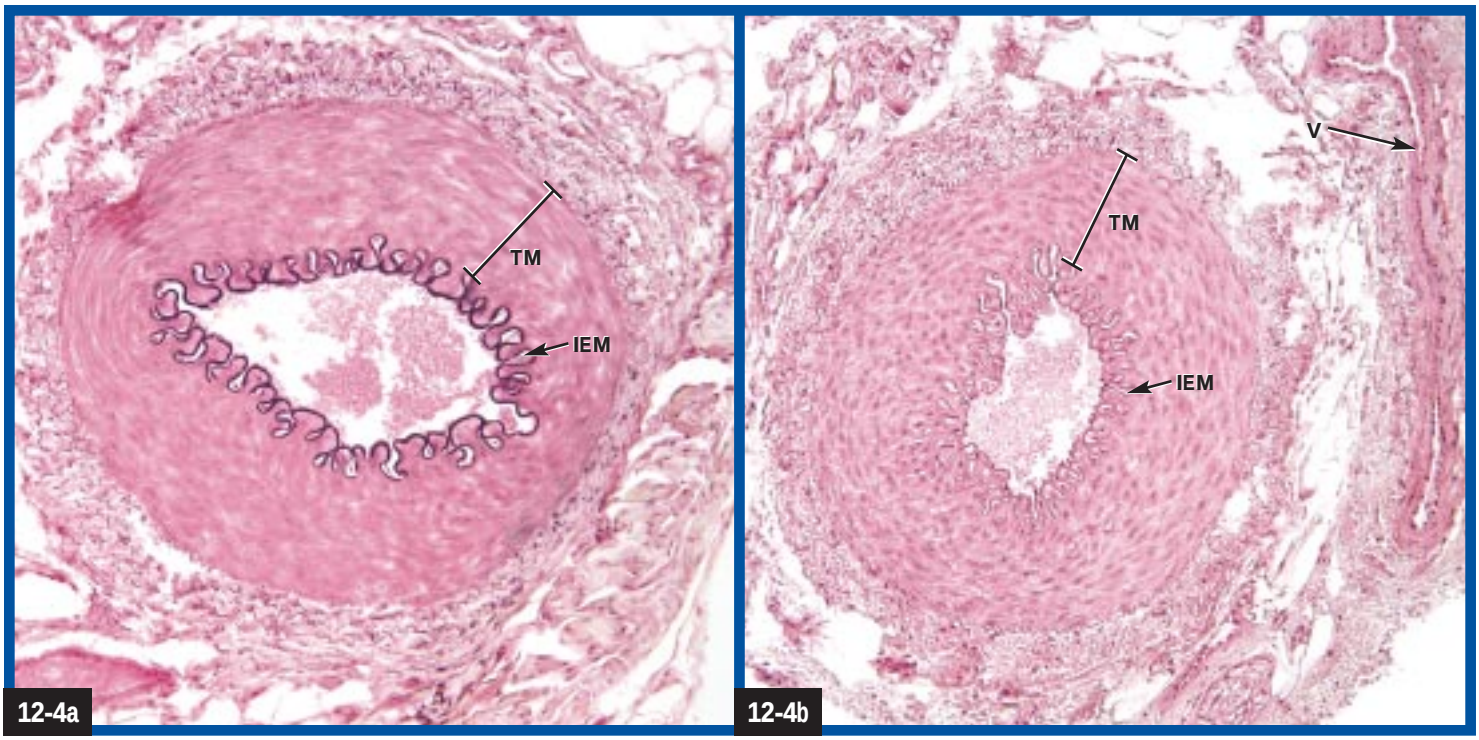
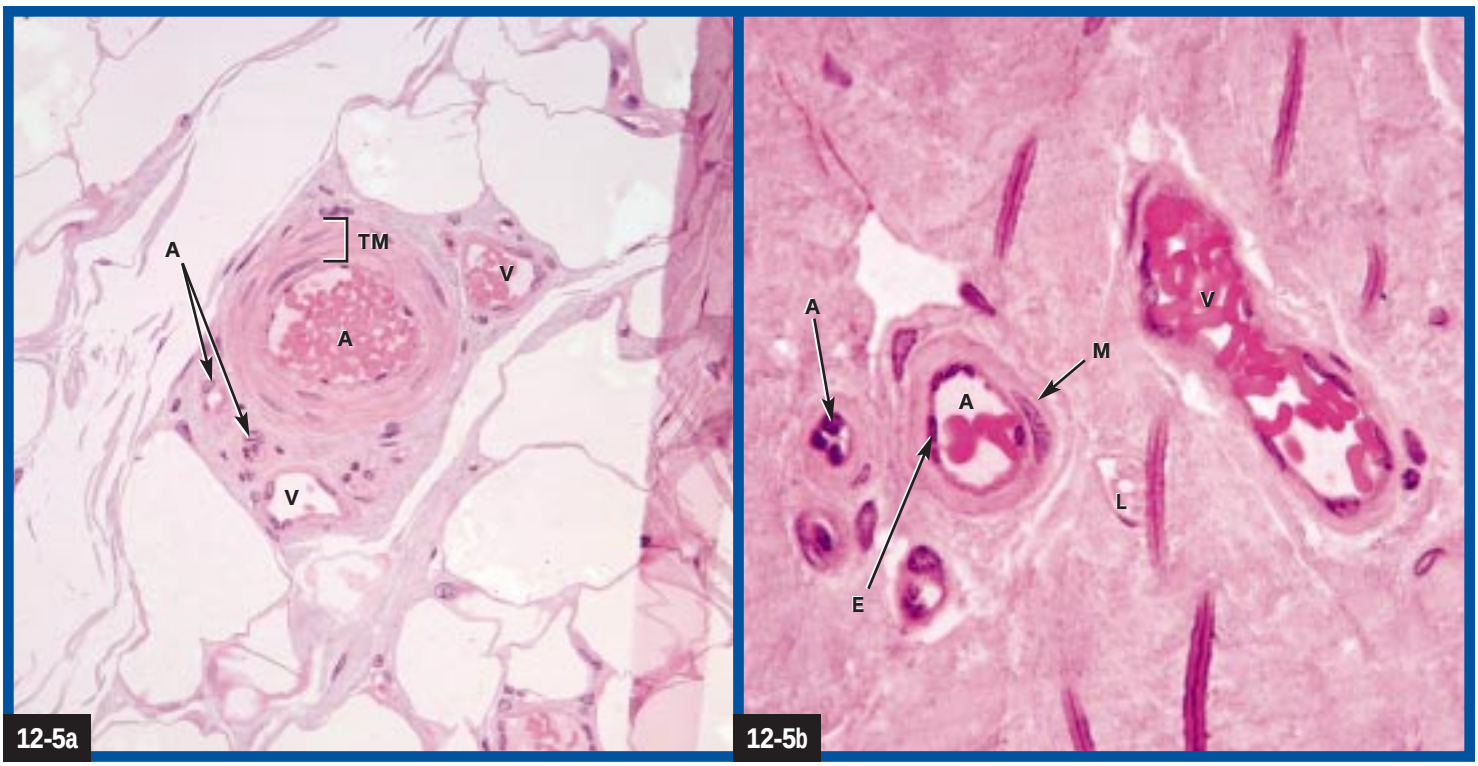


MUSCULAR ARTERY Medium sized arteries are also known as muscular arteries because of the abundance of smooth muscle fibers in the tunica media (TM). Notice in both specimens that the tunica media is the thickest layer, a feature typical of arteries in general. (a) In this specimen, the internal elastic membrane (IEM) is obvious as a dark squiggly line. (*X130*) (b) The internal elastic membrane is still very apparent in this micrograph even though it did not stain a color that makes it stand out. Also note the vein (V) at the right. *(X130)*



ARTERIOLE AND VENULE (a) Arterioles (A) are less than 200 µm in diameter. In this specimen, the endothelial lining and internal elastic membrane are visible and the tunica media (TM) is about three muscle cells thick. Notice that the tunica adventitia blends in with the surrounding connective tissue. Two smaller arterioles are also present, each with a single layer of smooth muscle. To the right and below the largest arteriole are two smaller venules (V). Note their thin walls. (*X265*) (b) In this specimen, the nuclei of smooth muscle cells (M) in the arterioles are larger and lighter than the endothelial cells' nuclei (E). Notice that the tunica media of the smallest arterioles consists of one layer of smooth muscle. The wall of the venule is extremely thin, but the lumen is relatively large. There is also a small lymphatic vessel (L) visible in the field. (*X660*)

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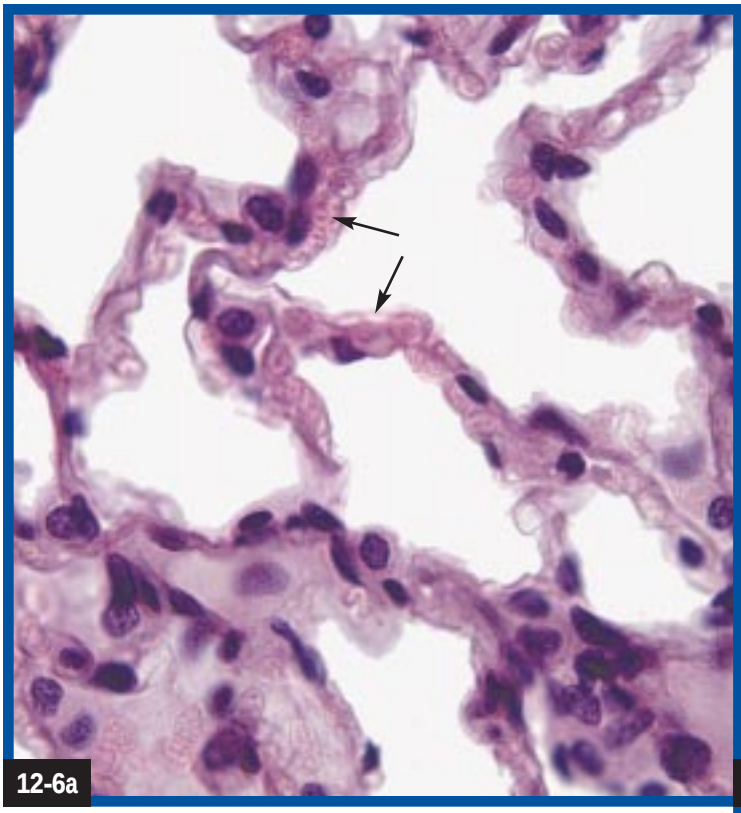

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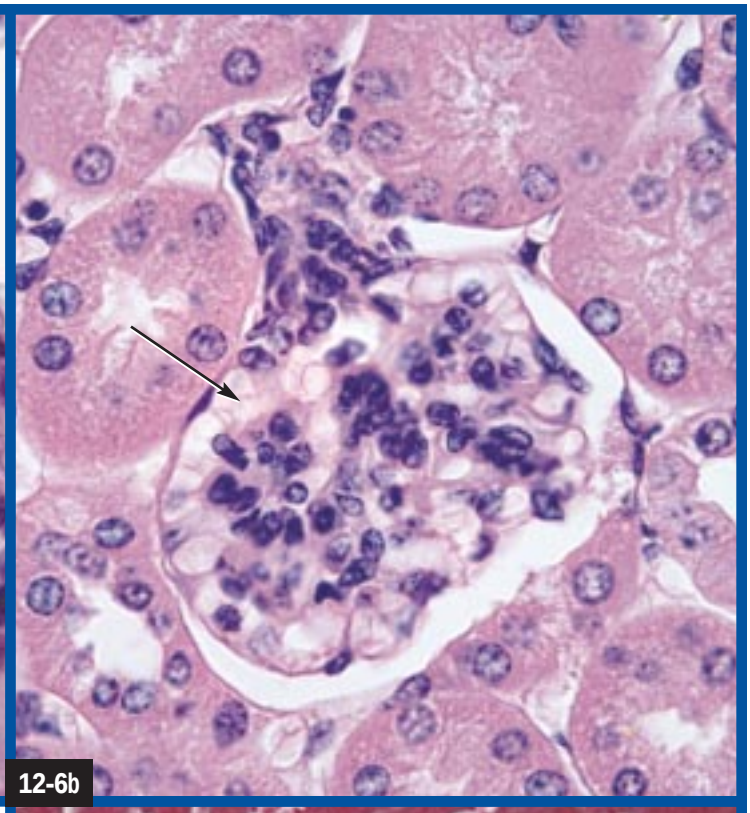

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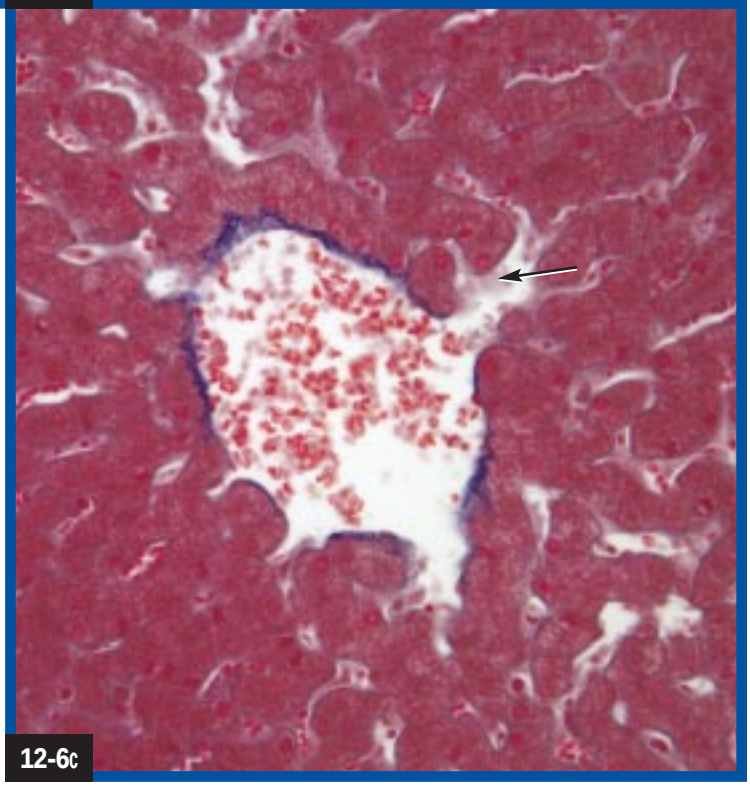

12-6c

CAPILLARIES Capillaries are the smallest of blood vessels and are the site of material exchange between the blood and tissues. They can be recognized by the wall consisting only of endothelium and the red blood cells often lining up in single file within the lumen. There are three types of capillaries recognized based on structures visible with the electron microscope. While they can't be differentiated using light micrographs, following are examples of each type. In each case, an arrow indicates the capillaries. (a) This lung specimen provides examples of continuous capillaries, the most abundant of the three. (*X660*) (b) Glomerular capillaries in the kidneys are an example of the fenestrated type. (*X660*) (c) This liver specimen provides an example of sinusoidal capillaries. These have an endothelium, but it is not complete. The cells around it determine the overall shape of the capillary. Notice that these are larger than the other capillary types as evidenced by the number of RBCs that fit across the diameter. *(X265)*

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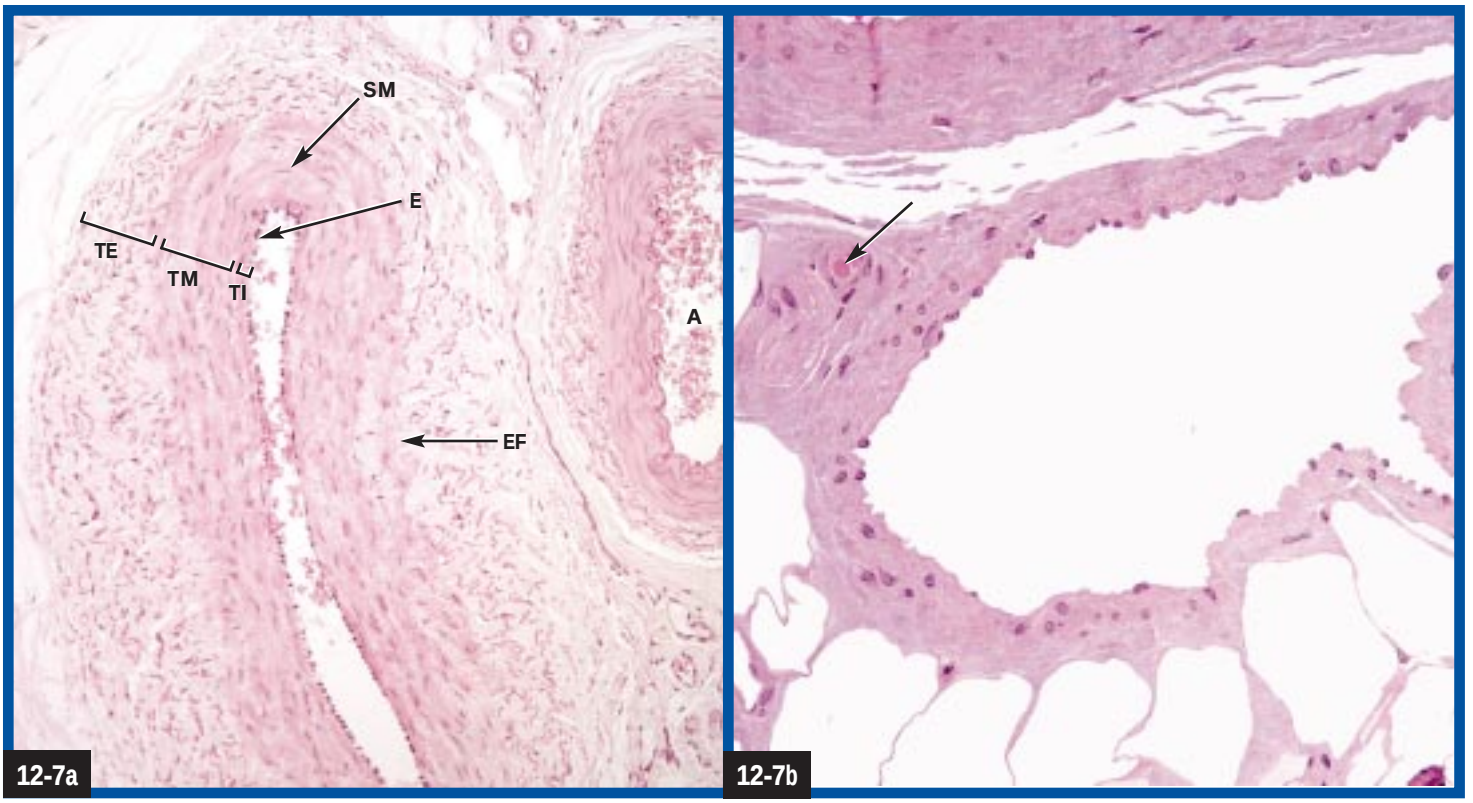
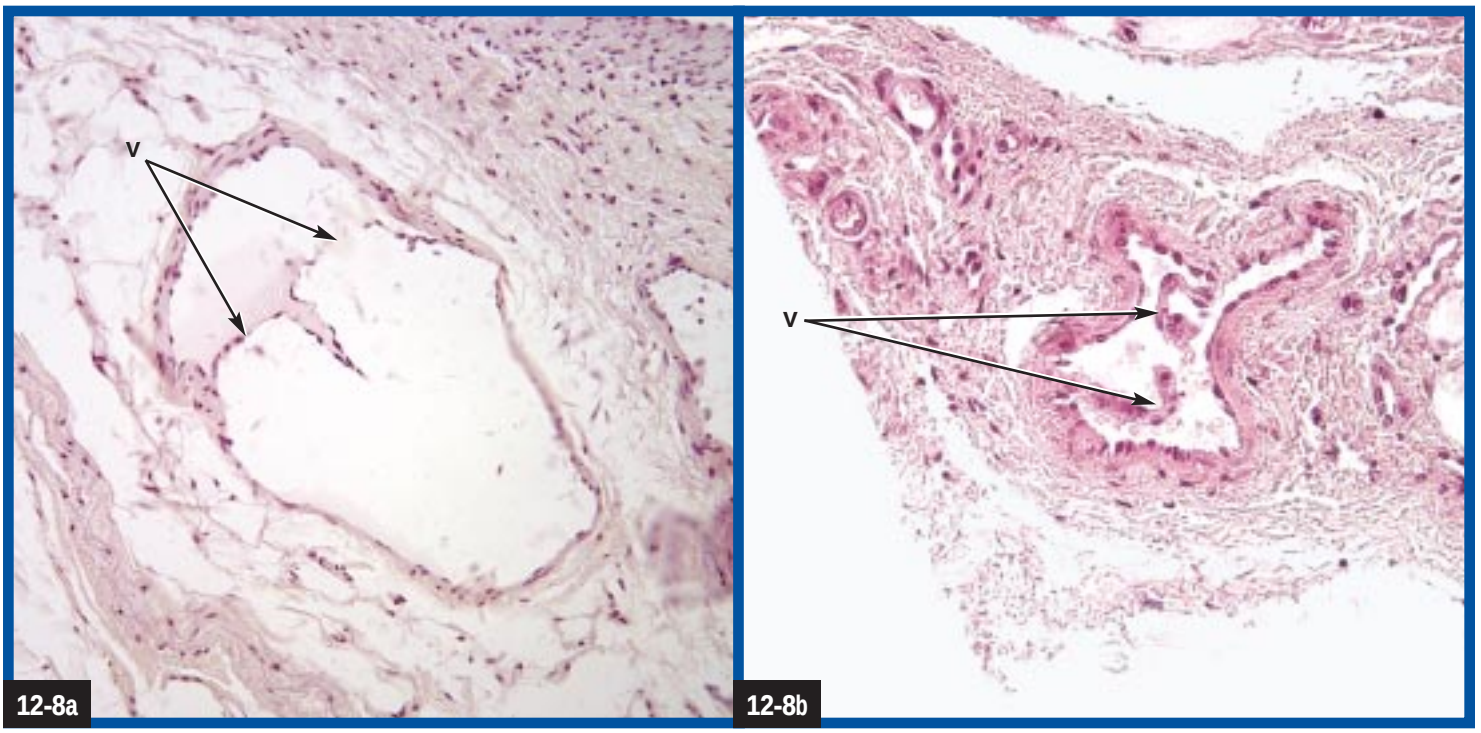


VEINS Veins are typically thin-walled and the tunica externa is the thickest layer. (a) This micrograph of a vein clearly shows the layers, which stain the same as the comparable layers in the artery (A). Notice the nuclei of the endothelial cells (E) in the tunica interna (TI), the smooth muscle (SM) of the tunica media (TM), and elastic fibers (EF) in the tunica externa (TE). (X125) (b) The layers are not as distinct in this micrograph of a small vein. Note the arteriole (arrow). *(X260)*



VALVES IN VEINS Veins carrying blood against gravity often have pocket-shaped valves (V) made of infoldings of tunica interna. (a) *X125* (b) *X260*.

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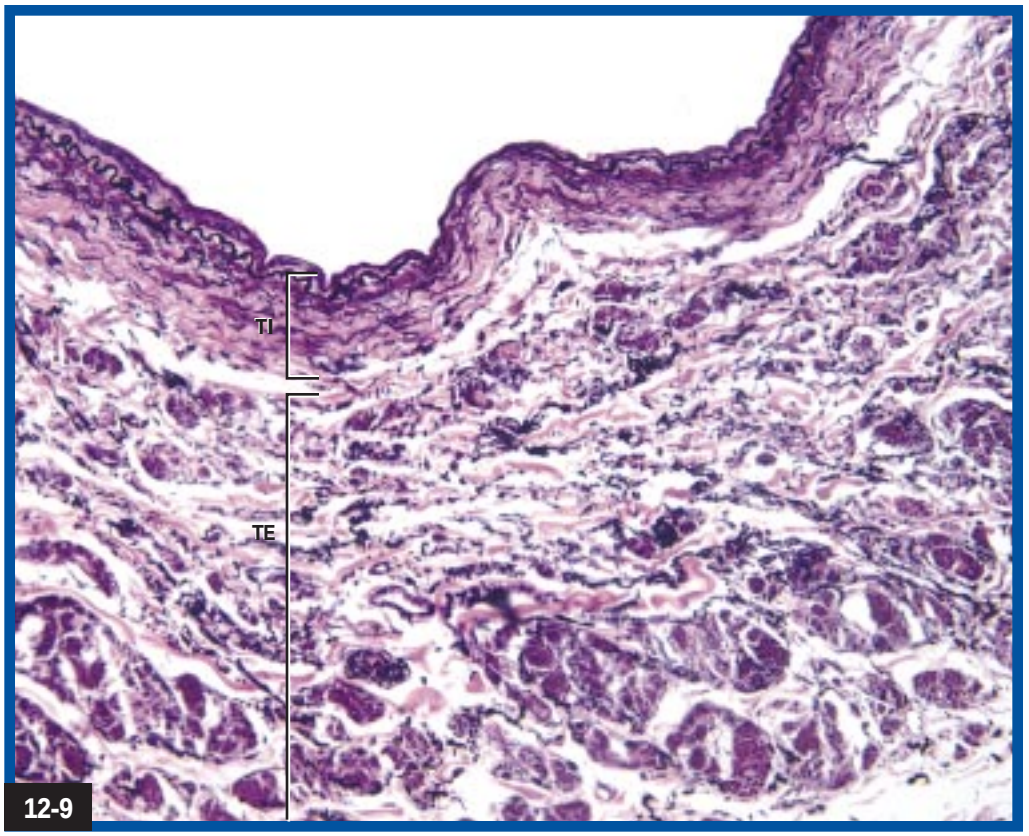
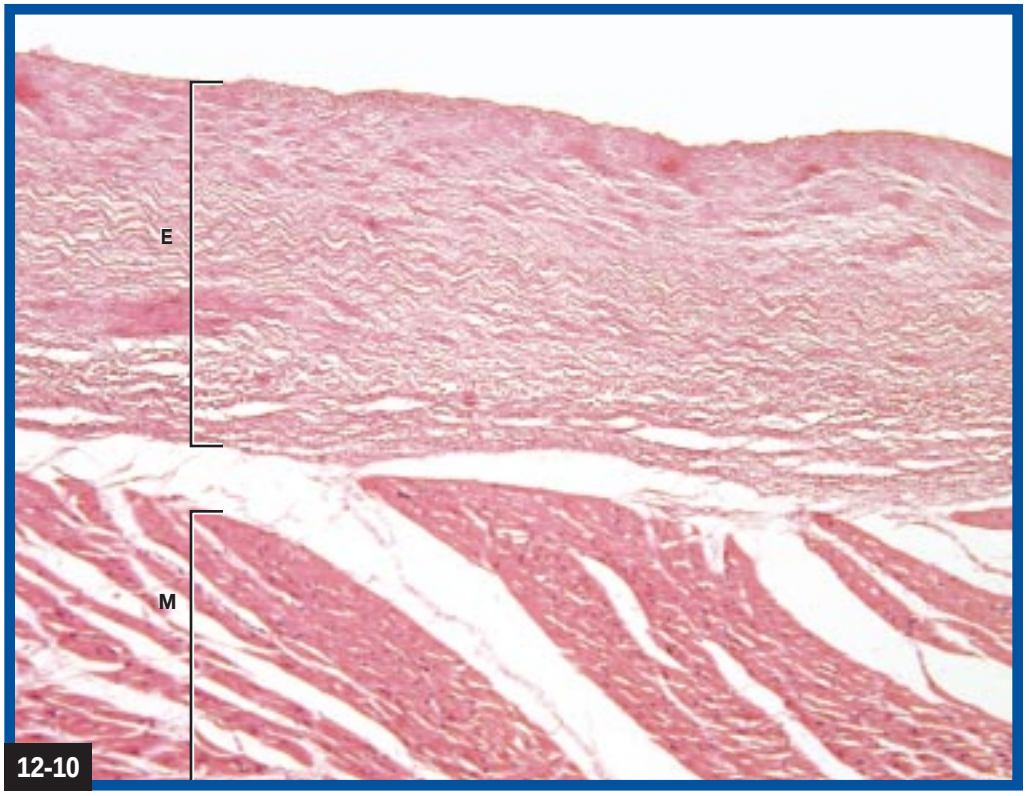


VENA CAVA Large veins have a thick tunica interna (TI) and tunica externa (TE). The tunica media is absent or not well-defined. *(X125)*



ENDOCARDIUM The inside of the heart is lined with endocardium composed of an endothelium and loose connective tissue. In this micrograph, the endocardium (E) and myocardium (M) are visible. *(X65)*

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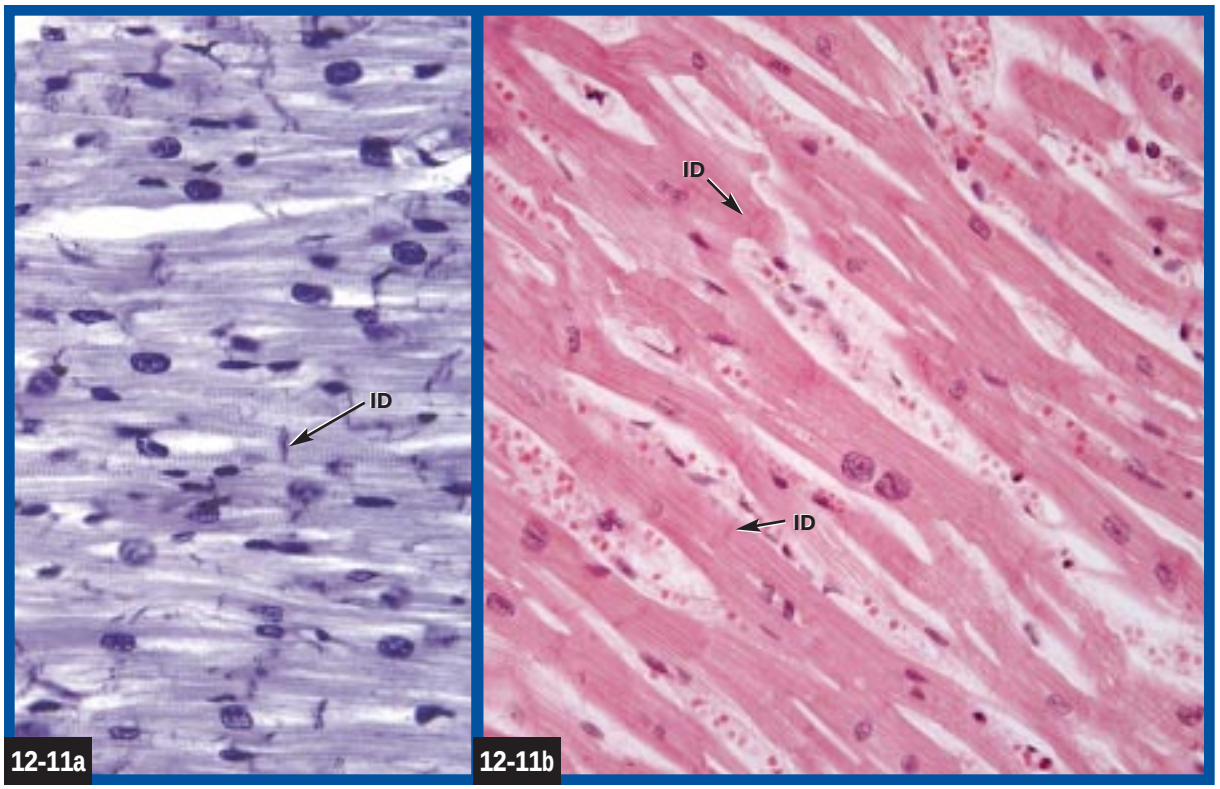
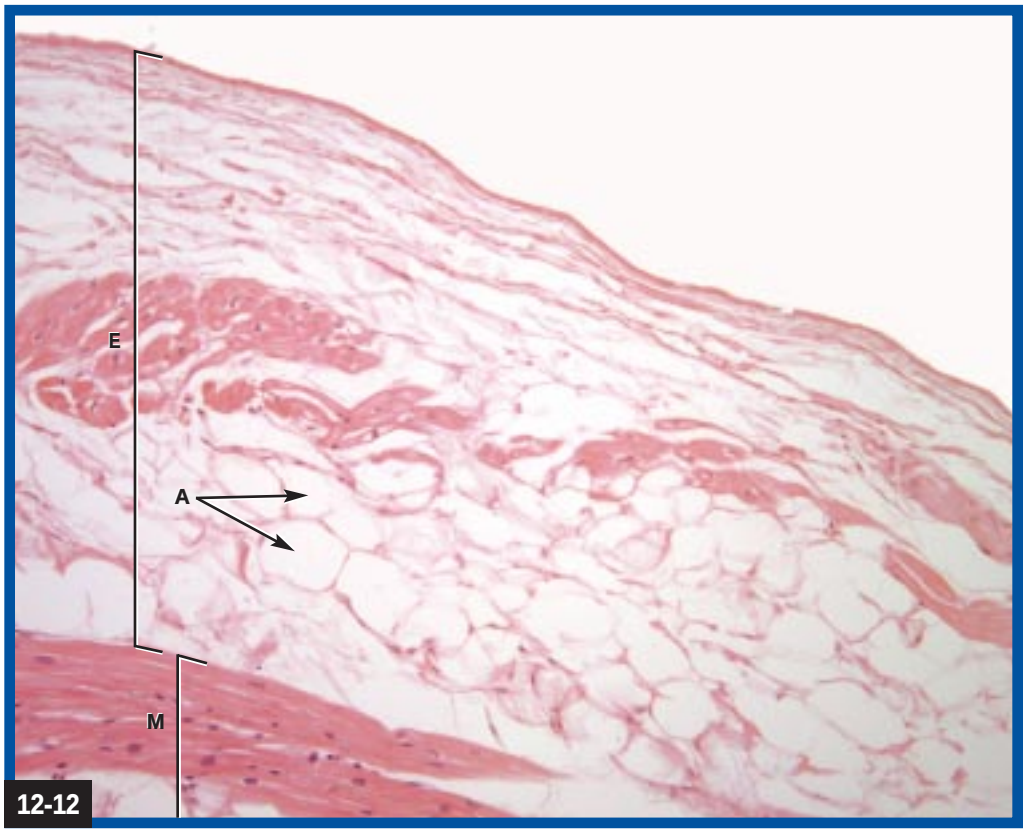


MYOCARDIUM The thickest layer in the heart's wall is the myocardium. Shown here are two micrographs of cardiac muscle prepared with different stains. In (a), the striations and intercalated discs (ID) are easily seen. (*X380*) In (b), striations are difficult to see and the intercalated discs are faint, but the branching fibers are very obvious. Notice the numerous capillaries (continuous type) between the fibers. *(X250)*



EPICARDIUM The outer surface of the heart is lined with serous membrane known as epicardium (E) or visceral pericardium. Notice the adipocytes (A) and myocardium (M). *(X130)*

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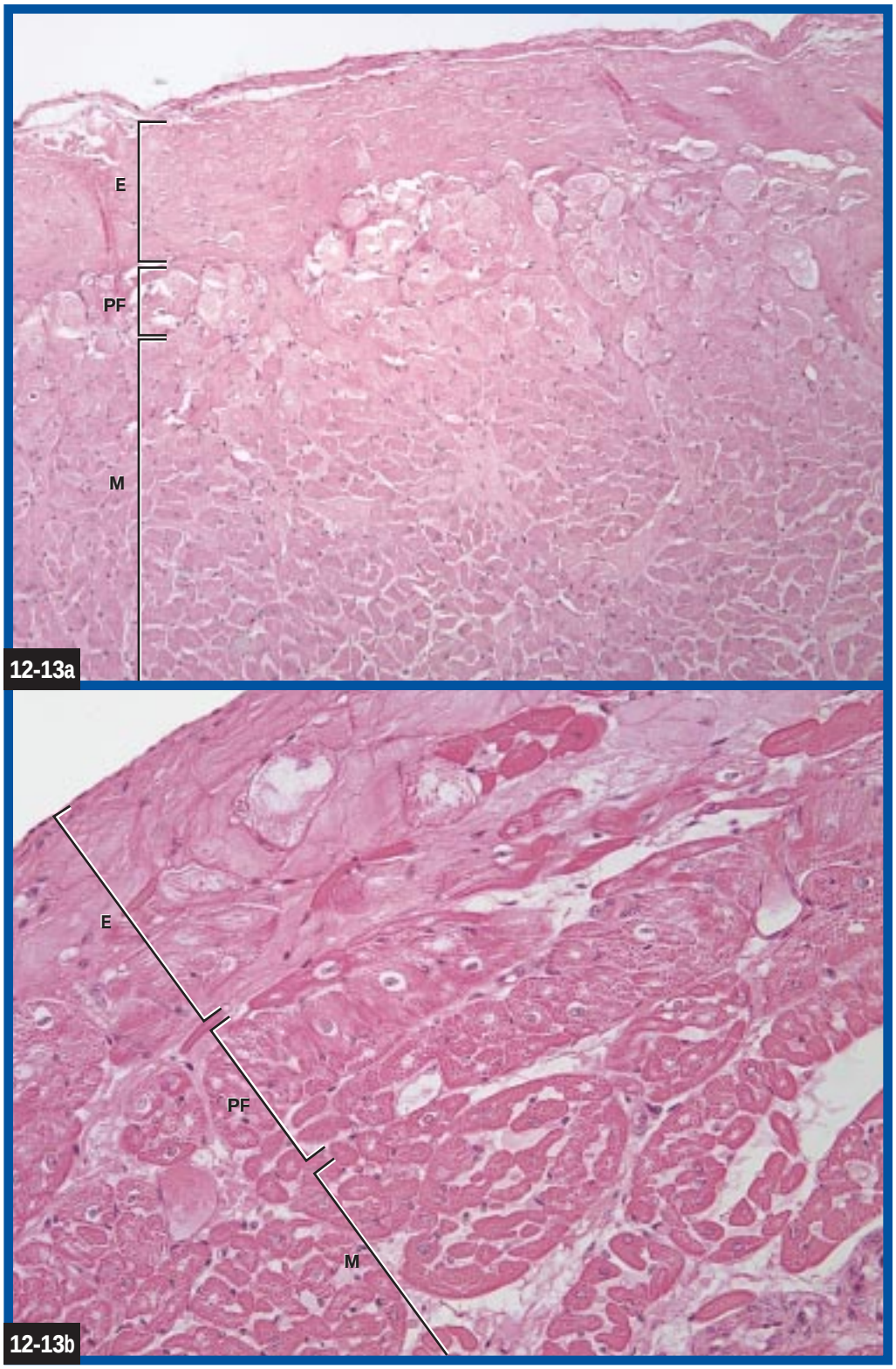

PURKINJE FIBERS Purkinje fibers (PF) are part of the heart's conducting system and are responsible for carrying the impulse from the apex upward across the ventricles. They are located between the endocardium (E) and myocardium (M). Purkinje fibers are modified cardiac muscle cells, but are larger and lighter staining. Both micrographs are *X130*.

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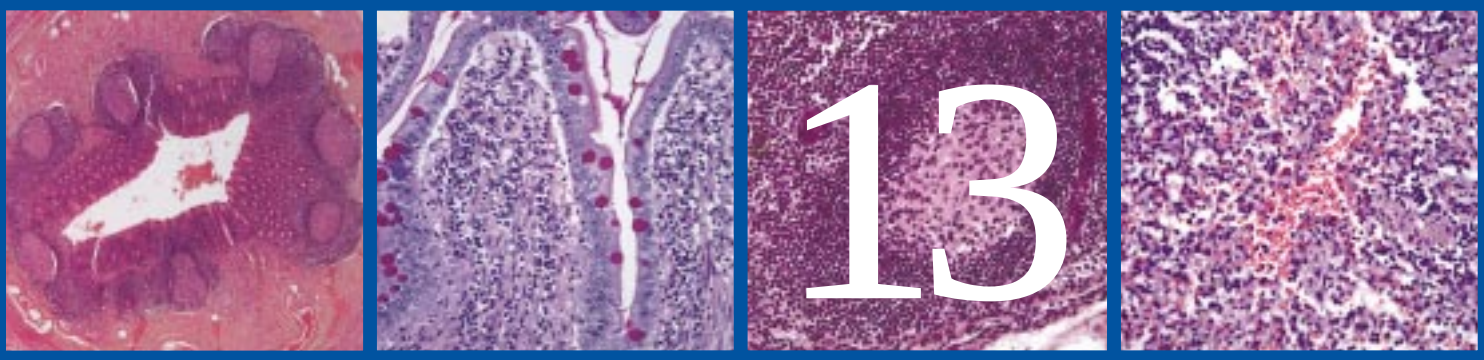
Lymphatic System

CHAPTER



13

Introduction to the Lymphatic System

The primary role of the lymphatic system is that of immunity, of allowing the body to differentiate between "self" and "nonself." Nonself chemicals or cells are broadly referred to as antigens. (Immunologists define antigens more precisely than that, but this definition will serve our purposes.) The body's response to an antigen is either **humoral**, in which antibodies are secreted into tissue fluids, or **cellular**, in which the defense is provided directly by the immune cells. In either case, the response is specific for each antigen.

The lymphatic system is also involved in recovery and transport of tissue fluid, as well as absorption of fats in the small intestine.

Cells of the Immune System

There are several types of immune cells, but they are mostly difficult to differentiate with the light microscope. The following relies on identification by sophisticated techniques that are beyond the scope of an introductory histology course, as is an exhaustive description of their functions. For more information, the reader is referred to an immunology text.

Lymphocytes (Figure 13-1) constitute approximately 20–25% of all leukocytes seen in the blood. They are typically about the size of erythrocytes, but larger lymphocytes are also seen. Lymphocytes are categorized into one of three functional groups: B cells, T cells, and NK cells. When functional, they are not found in the blood, but rather in lymphoid organs or as aggregations in extravascular tissues.

B cells possess an antigenic marker that identifies them. They are produced in the bone marrow and also become immunocompetent there. When stimulated, the appropriate B cell multiplies and differentiates into **plasma cells** and **memory B cells**. Plasma cells actively secrete antibodies (humoral immunity), whereas memory cells remain dormant until subsequent contact with the same antigen. Plasma cells are elongated and have nuclear chromatin resembling a clock face. A light region near the nucleus is the site of the Golgi apparatus. Memory B cells are indistinguishable from other lymphocytes in routine histological preparations.

T cells are produced in the bone marrow but become immunocompetent in the thymus. They are identified by a T cell antigenic marker and are involved in cell mediated responses. When stimulated, T cells proliferate and differentiate into one of several functional groups. **T helper (T_H) cells** assist other T cells or B cells in their immune response. **Cytotoxic T (T_c) cells** are active in killing foreign cells or virally infected cells. **Memory T (T_M) cells** perform the same function as their B cell counterparts. These T cells are indistinguishable from other lymphocytes in routine histological preparations.

Natural killer (NK) cells are large lymphocytes that lack the T and B cell antigenic markers, and as such belong to the population of **null cells**. NK cells kill cells coated with antibodies in a process called antibody-dependent cell-mediated cytotoxicity.

Another category of cells involved in the immune response are **antigen presenting cells (APCs)**, which are involved in processing an antigen and "showing" it to the

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appropriate immune cell to begin the immune response. **Macrophages** (Figure 4-9) and **dendritic (Langerhans) cells** (Figure 11-3c) of the skin are examples.

Organs of the Lymphatic System

Lymphatic tissue is found in encapsulated lymphoid organs, such as lymph nodes, the thymus, and the spleen, and also as unencapsulated clusters in the walls of other organs such as those of the digestive and respiratory tracts.

Thymus

The **thymus** (Figure 13-2) is found in the mediastinum, the region of the thoracic cavity between the lungs. It is most highly developed at puberty, then is replaced with adipose tissue as the individual ages. A dense connective tissue **capsule** covers the thymus, and connective tissue **trabeculae** or **septa** arising from it divide the organ's two lobes into **lobules**. The outer portion is the **cortex** and the inner part is the **medulla**.

The **thymic cortex** (Figure 13-3) stains darker and more basophilic than the medulla, and is occupied by numerous T lymphocytes **(thymocytes)** that have migrated from the bone marrow. They proliferate and as they mature, they move toward the medulla. They become immunocompetent at the periphery of the cortex. **Epithelial reticular cells** separate the cortex from the blood vessels in the trabeculae and form the blood-thymus barrier that prevents antigens from contacting thymocytes.

The **thymic medulla** (Figure 13-4) is eosinophilic and has fewer lymphocytes and more epithelial reticular cells than the cortex. From the medulla, mature T cells enter blood or lymphatic vessels and spread throughout the body to populate other lymphatic organs. **Thymic (Hassall's) corpuscles** are the most distinctive features of the medulla. They are concentrically arranged keratinized epithelial reticular cells. Their function is unknown, but they probably are produced by a degenerative process.

Lymph Nodes and Lymph Vessels

Lymphatic vessels (Figure 13-5) return tissue fluid to the blood vascular system. The lymph vasculature begins as blind capillaries consisting of a simple squamous endothelium. The capillaries are tributaries to small lymph vessels, which continue to converge and get larger. Ultimately, lymph vessels empty into the right lymphatic duct and the thoracic duct, which drain lymph into the right and left subclavian veins, respectively. On slides, RBCs are not seen in lymph vessels, but lymphocytes may be present.

In addition to their pattern of convergence, lymph vessels also resemble veins in being thin-walled (but thinner) and having valves. The tunics are indistinct in most lymph vessels, but the tunica media of the lymphatic ducts has longitudinal and circular layers of smooth muscle in it.

Lymph nodes (Figure 13-6) are located periodically along the length of lymph vessels. B and T cells, as well as macrophages, populate them. Antigens in tissue fluid enter the lymph and are removed by these cells before they can get into the blood.

Lymph nodes are bean-shaped and are covered with a dense connective tissue **capsule**. **Afferent lymph vessels** carry lymph to the node and enter along the node's convex surface. The indentation is the **hilus** and is the point of entry and exit for blood vessels, as well as exit of the **efferent lymph vessel** (Figure 13-7).

Internally, the node is divided by extensions of the capsule called **trabeculae** (Figure 13-8). Connecting the afferent vessels with the efferent vessel is a series of channels called sinuses, each named according to its location. The **subcapsular sinus** is on the periphery of the node, and the **cortical** and **medullary sinuses** are in the node's cortex and medulla, respectively. As lymph passes through the sinuses, it contacts the immune cells inhabiting the node.

Most lymphocytes enter the node through the artery, with the remainder entering through the afferent vessels. A framework of reticular fibers coursing through the node supports them. In the cortex, lymphocytes are found in dense, spherical clusters called **lymph follicles** or **lymph nodules** (Figure 13-9). **Primary follicles** are uniform in appearance and are mostly composed of small, inactive B cells. **Secondary follicles** have a light staining **germinal center** composed of proliferating B cells surrounded by a darker **mantle zone** populated by inactive B cells. A lighter **marginal zone** may be seen around the mantle zone. T lymphocytes dominate the deepest portion of the cortex called the **paracortex**. Follicles are not found in the paracortex. Lymphocytes of the medulla are organized into elongated **cords** (Figure 13-10). The cells are primarily plasma cells and B lymphocytes.

The mantle zone of a secondary follicle is often wider on the side near the capsule. Likewise, the germinal center shows polarity, with the medullary side being darker (the **dark zone**) than the side facing the capsule (the **light zone**). It is in the germinal center that B cells divide and produce plasma cell precursors and memory B cells. The memory B cells enter circulation and take up residence in other lymphatic tissues whereas the plasma cell precursors move to the medullary cords and finish their differentiation.

Spleen

The spleen is a lymphoid organ that occupies the left upper quadrant of the abdominal cavity. It is responsible for immune responses to blood antigens as well as phagocytosis of worn out RBCs and other particulate matter.

The **capsule** (Figure 13-11) is composed of fibrous connective tissue and smooth muscle. Connective tissue **trabeculae** penetrate the spleen from the capsule and reticular fibers form a framework in which the lymphocytes are suspended.

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Spleen tissue is divided into **red pulp** and **white pulp**. Red pulp (Figure 13-12) is the blood vascular component and includes blood **sinuses** and the intervening **splenic cords** composed of macrophages, lymphocytes, and blood cells. The sinuses are made of endothelium and are enveloped in reticular fibers. White pulp (Figure 13-13) is composed of lymphocyte aggregates. T cells form **periarterial lymphatic sheaths (PALS)** around the **central arteries**. The other type of white pulp is made primarily of B cells in lymph follicles with germinal centers and mantle zones. A lighter marginal zone of active macrophages is found at the periphery of the follicle.

Other Unencapsulated Lymphatic Tissue

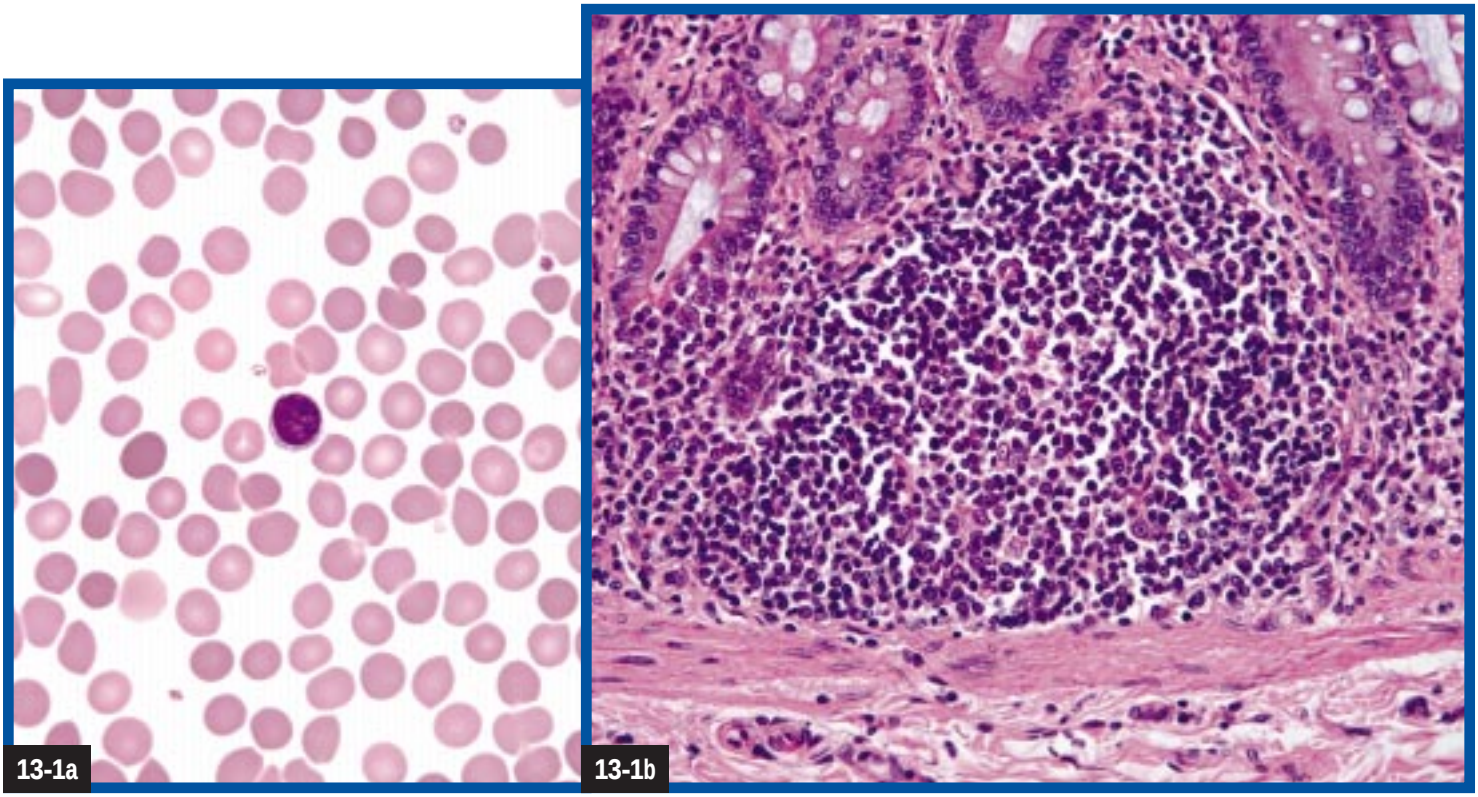
Lymphatic tissue is found scattered in various organs. In some cases, the lymphocytes are just dispersed in other connective tissues. In other cases they are organized into lymph follicles.

Scattered lymphocytes in the lamina propria and epithelium of various organs constitutes the **Mucosa Associated Lymphatic Tissue (MALT)**. T cells are the primary occupants of MALT, but some B cells are also present (Figure 13-14).

Tonsils are probably the most well known examples of MALT. They are small aggregations of unencapsulated lymphatic tissue located in the oropharynx and nasopharynx. The two **palatine tonsils** (Figure 13-15) are located at the junction of the oral cavity and the oropharynx. They consist of lymph follicles, mostly with germinal centers. The stratified squamous epithelium of the oral mucosa covers them and penetrates downward as **tonsilar crypts**. Dendritic cells in the epithelium act as APCs. Connective tissue **trabeculae** are present and there is a deep connective tissue capsule, but the tonsils are not surrounded by it. The **pharyngeal tonsil** (Figure 13-16) is located in the nasopharynx. It is covered with PSCC and some stratified squamous epithelium. There are no crypts, but the mucosa is folded into **pleats**. The **lingual tonsils** (Figure 13-17) are at the base of the dorsum of the tongue. They are covered with stratified squamous epithelium. Each has a single crypt.

Gut Associated Lymphatic Tissue (GALT) is composed of lymph follicles in the walls of digestive organs (Figure 13-18). They are most abundant in the **Peyer's Patches** of the ileum. GALT is drained by efferent lymph vessels, but has no afferent vessels. Instead, special epithelial cells called **M cells** overlie the follicles and transfer antigens to macrophages in the follicles which in turn present them to T cells. GALT is also abundant in the colon and the **vermiform appendix**, a tubular extension of the cecum.

Bronchus Associated Lymphatic Tissue (BALT) is common at the branch points of the respiratory tree, where M cells replace the respiratory epithelium (Figure 13-19). B cells are the most abundant cells, but APCs and T cells are also present.



LYMPHOCYTES (a) Lymphocytes are the second most abundant leukocyte in blood. *(X660)* (b) Lymphocytes are found in blood, but they are usually functional outside the blood stream. Shown here is a spherical aggregation of lymphocytes in the wall of the digestive tract. Each tiny purple dot is a lymphocyte. *(X260)*

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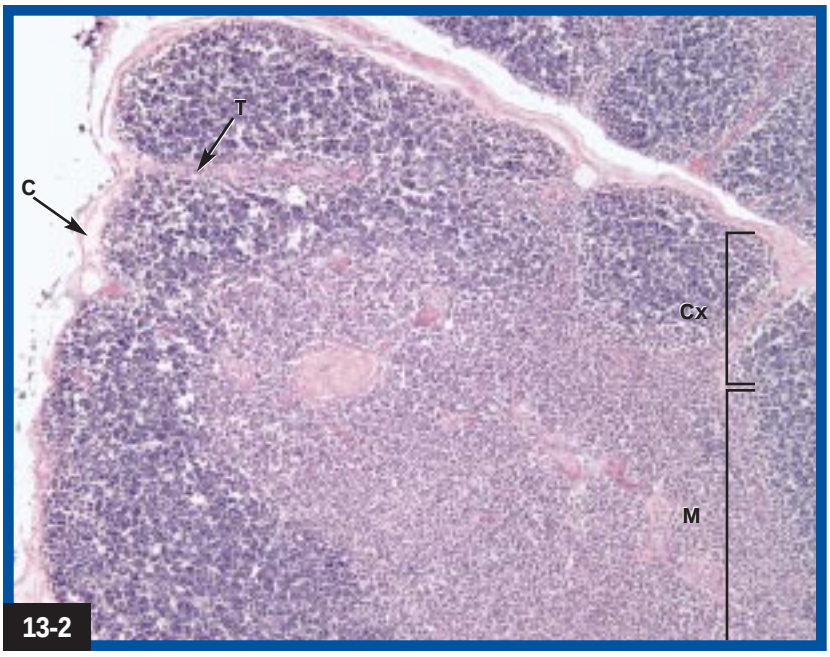
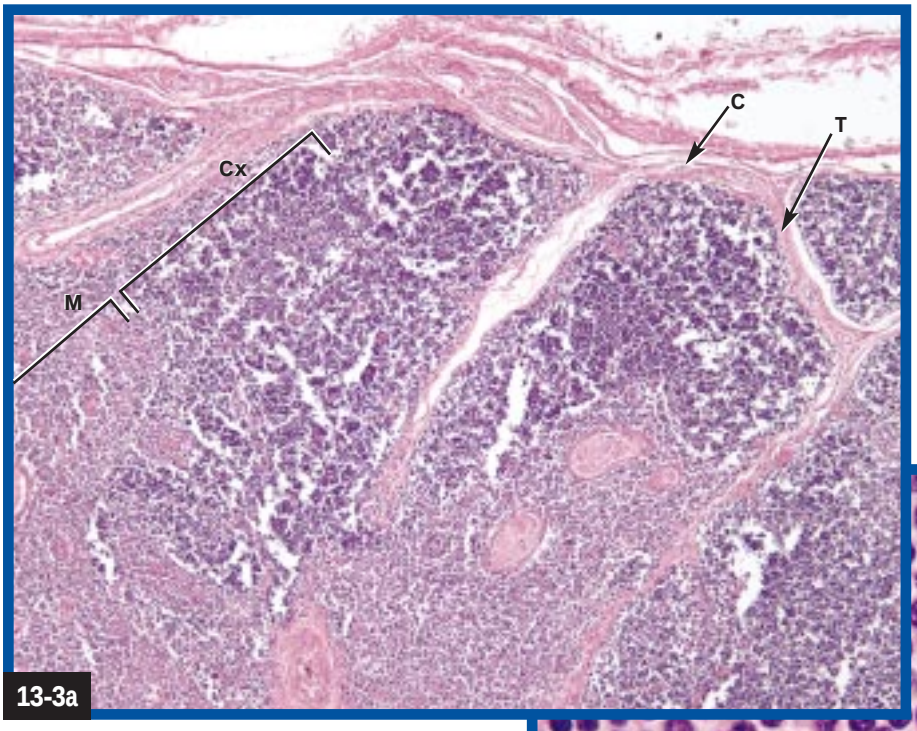
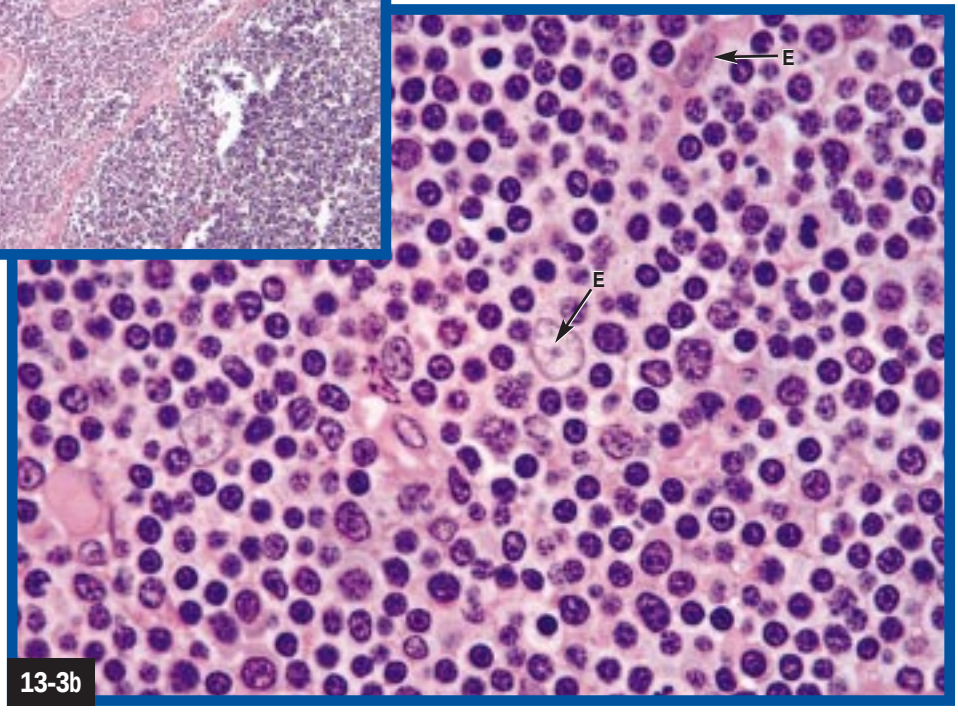


THYMUS The thymus is covered with a connective tissue capsule (C). Trabeculae (T) are projections of the capsule into the thymus that divide it into lobules. The cortex (Cx) and medulla (M) are clearly seen. *(X50)*





THYMIC CORTEX The outer region of the thymus is called the cortex. (a) In this micrograph, the capsule (C) and trabeculae (T) are visible. The more basophilic cortex (Cx) stands out against the more eosinophilic medulla (M). *(X60)* (b) Most of the cortical cells are thymocytes (T lymphocytes). Other cells of the cortex are macrophages and epithelial cells (E—these are difficult to see in normal preparations because of the numerous thymocytes). T cells that react with "self" die and are removed by the macrophages. *(X660)*

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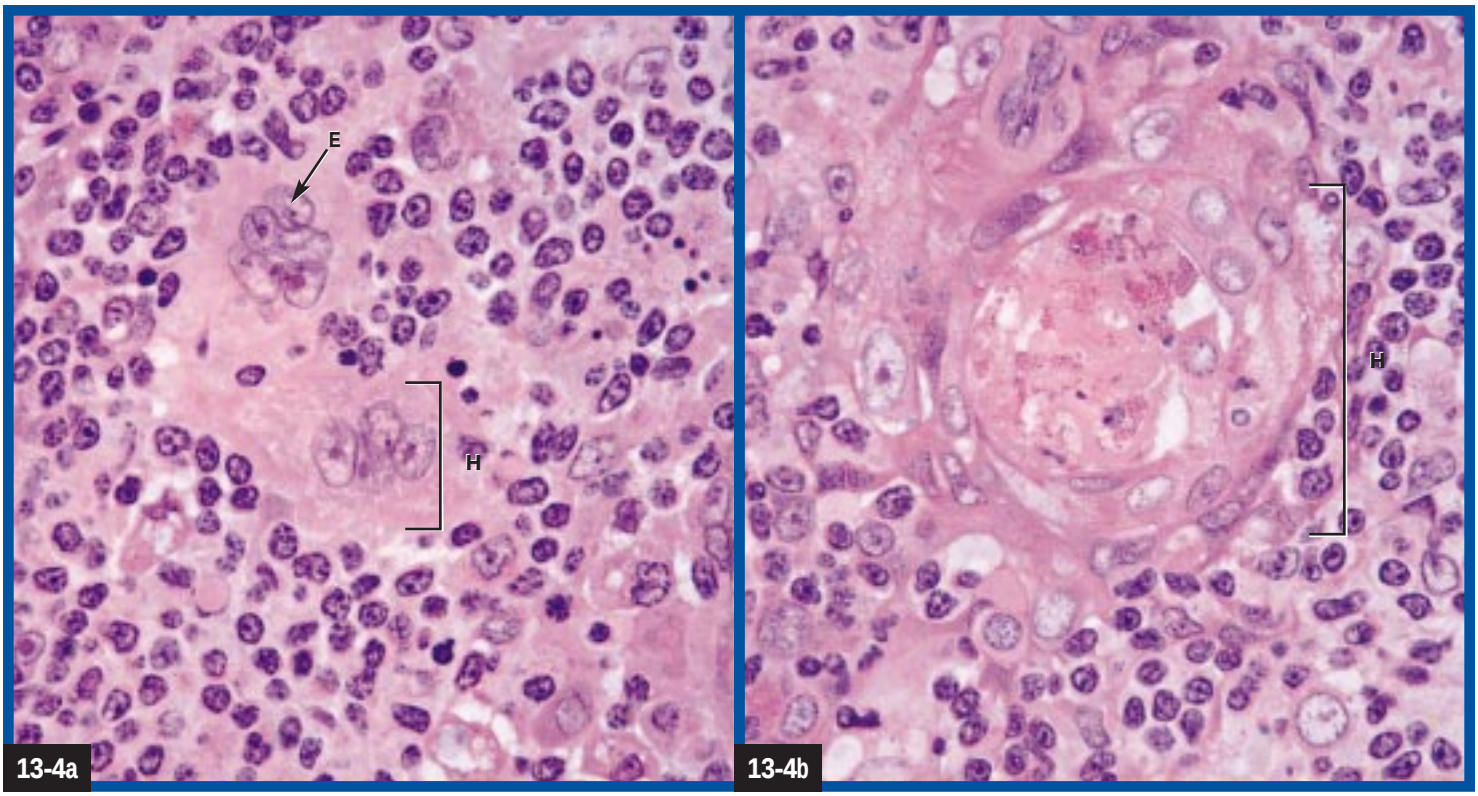
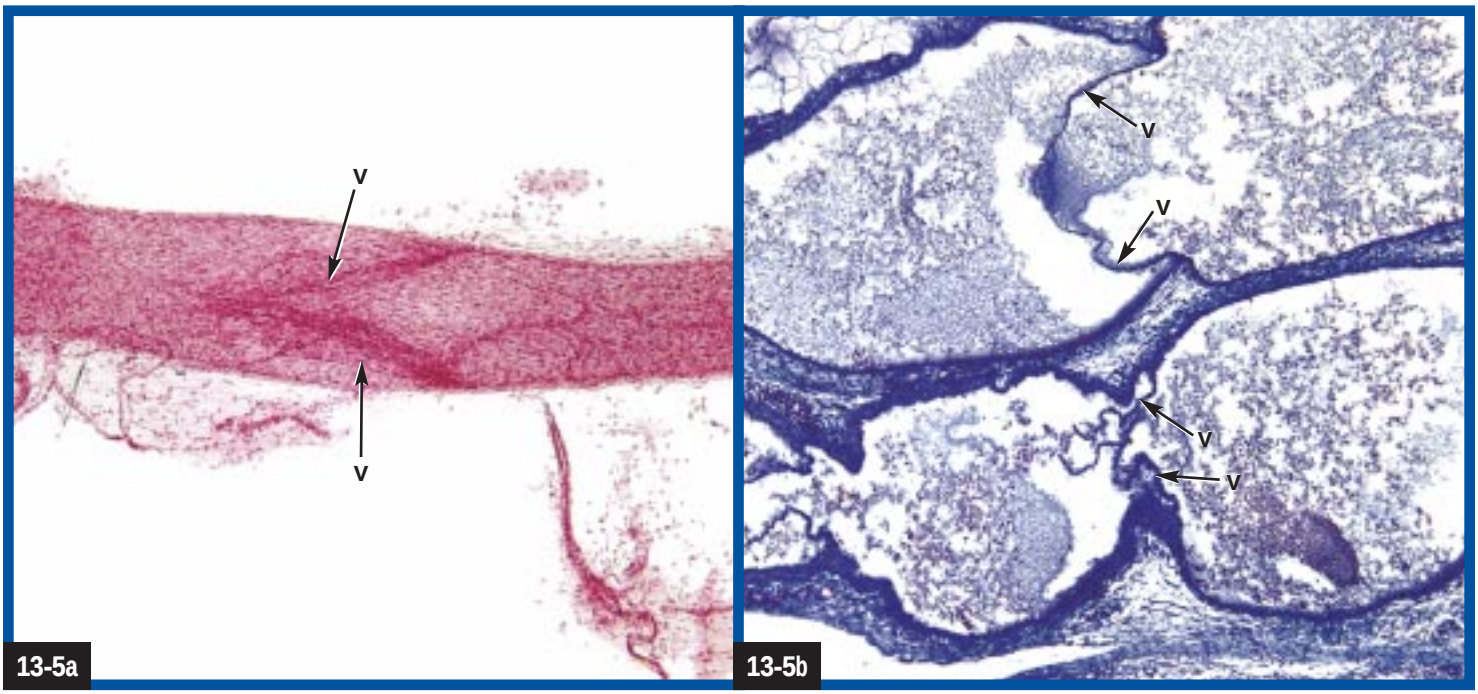


THYMIC MEDULLA Epithelial cells (E) involved in the positive and negative selection process of T cells are more visible in the medulla. They are rounded and light staining. Keratinized clumps of dying epithelial cells form Hassall's corpuscles (H), a distinctive feature of the thymus. (a) Epithelial cells and an early Hassall's corpuscle are seen in this micrograph. (*X660*) (b) A more advanced Hassall's corpuscle is shown in this micrograph. Epithelial cells are also visible. *(X660)*



LYMPH VESSELS Like veins, lymph vessels have valves, but they have thinner walls. (a) In this whole mount, the valve (V) and thin wall are apparent. (*X60*) (b) This is a section through a couple of lymph vessels with valves. *(X65)*

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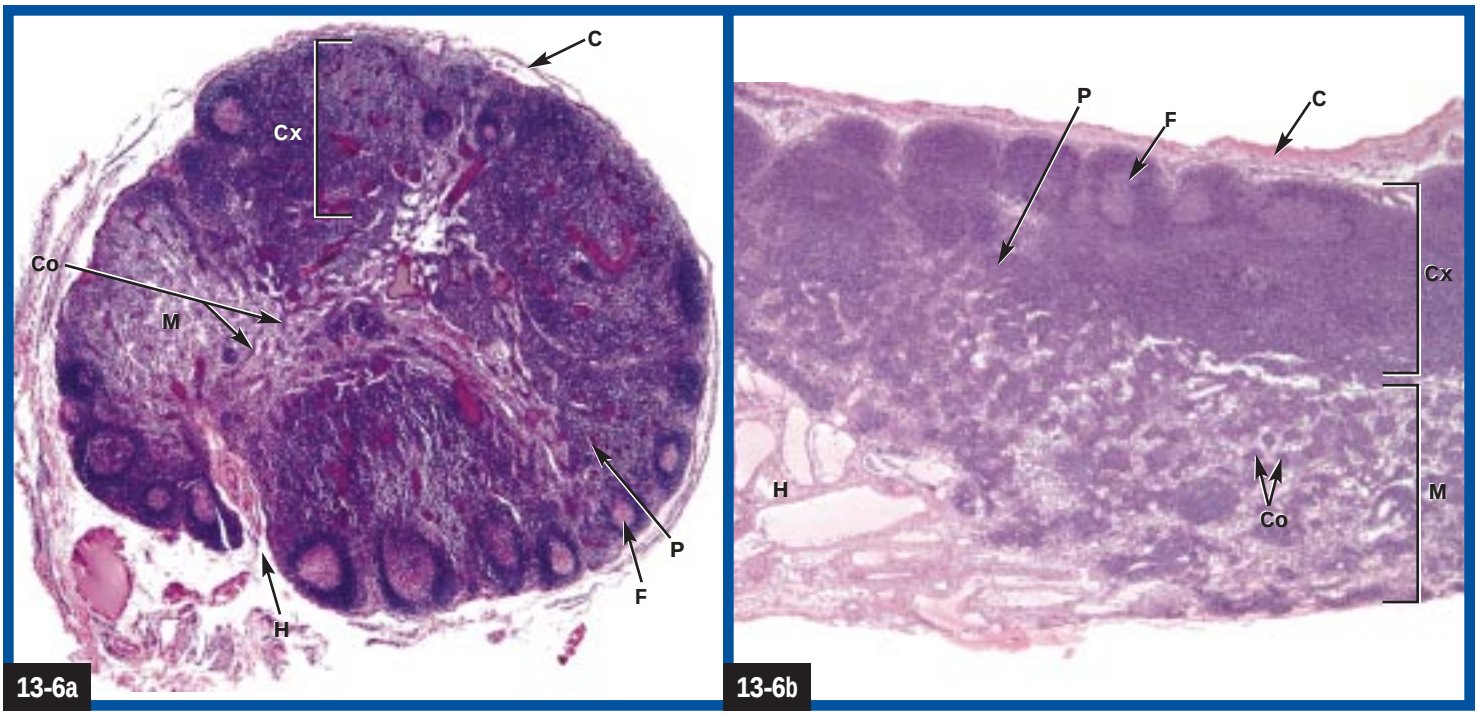
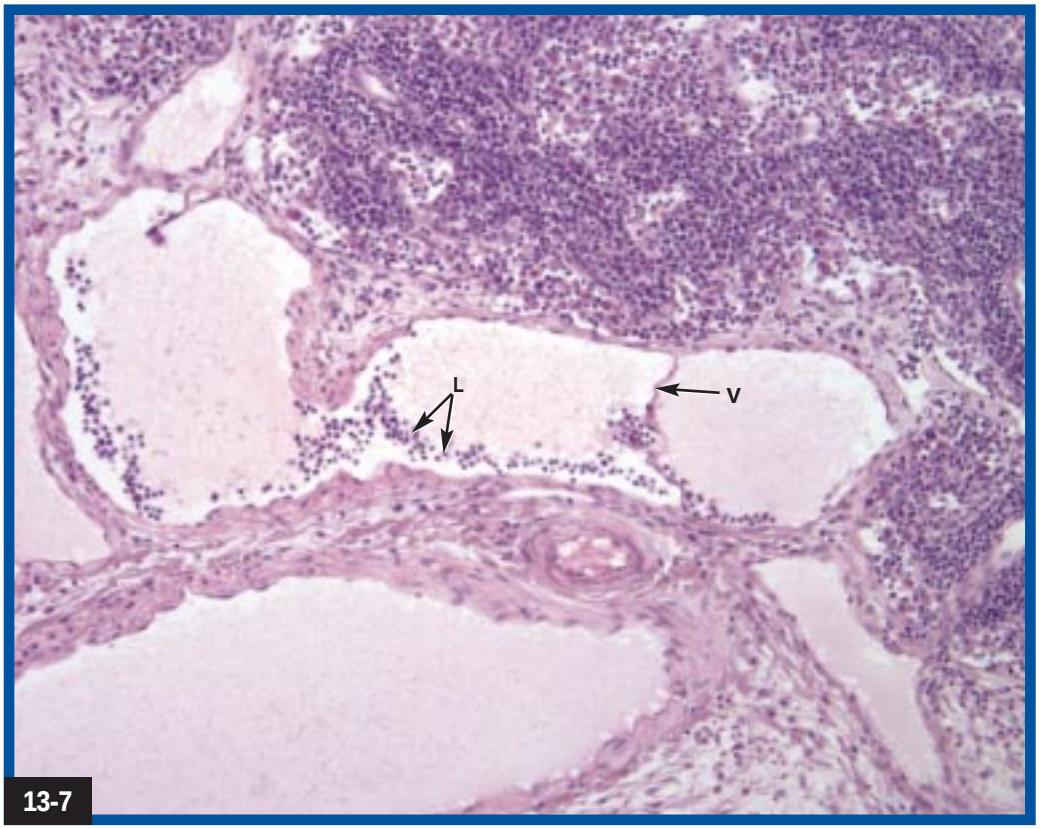


LYMPH NODE Each lymph node is covered by a connective tissue capsule (C). Lymphatic tissue comprising the cortex (Cx) is arranged in spherical follicles (F) or in irregular masses in the paracortex (P), whereas it is organized into cords (Co) in the medulla (M). Sinuses run between masses of lymphatic tissue. Blood vessels and efferent lymph vessels connect at the hilus (H). (a and b) Both micrographs are panoramic views of lymph nodes. *(X22)*



EFFERENT LYMPH VESSELS In this micrograph, efferent lymph vessels emerging from the hilus are visible. Note the valve (V), the lymphocytes (L), and the absence of RBCs in the vessel. *(X130)*

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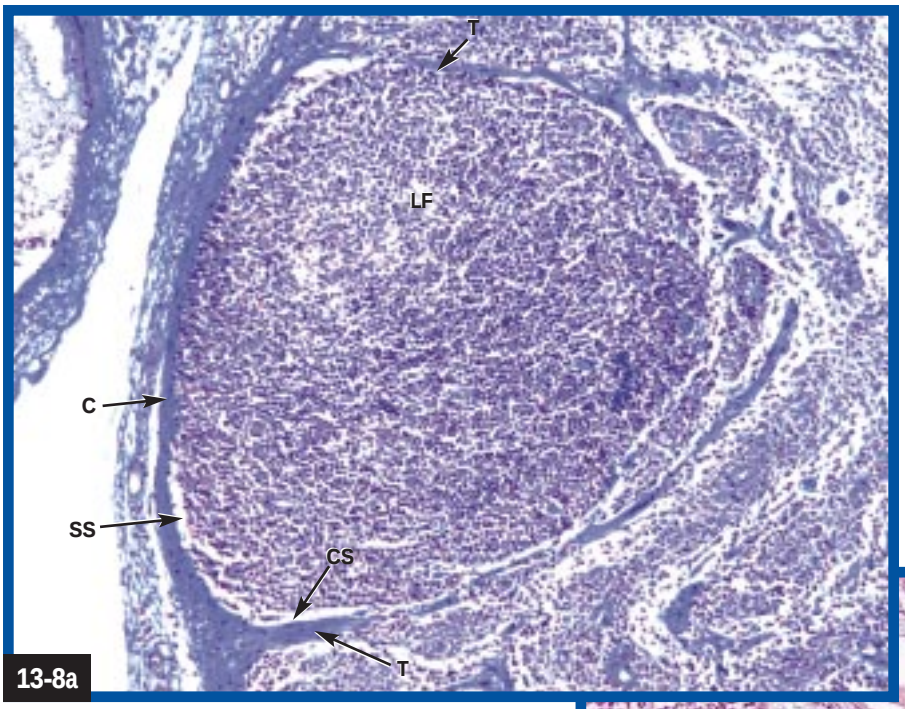

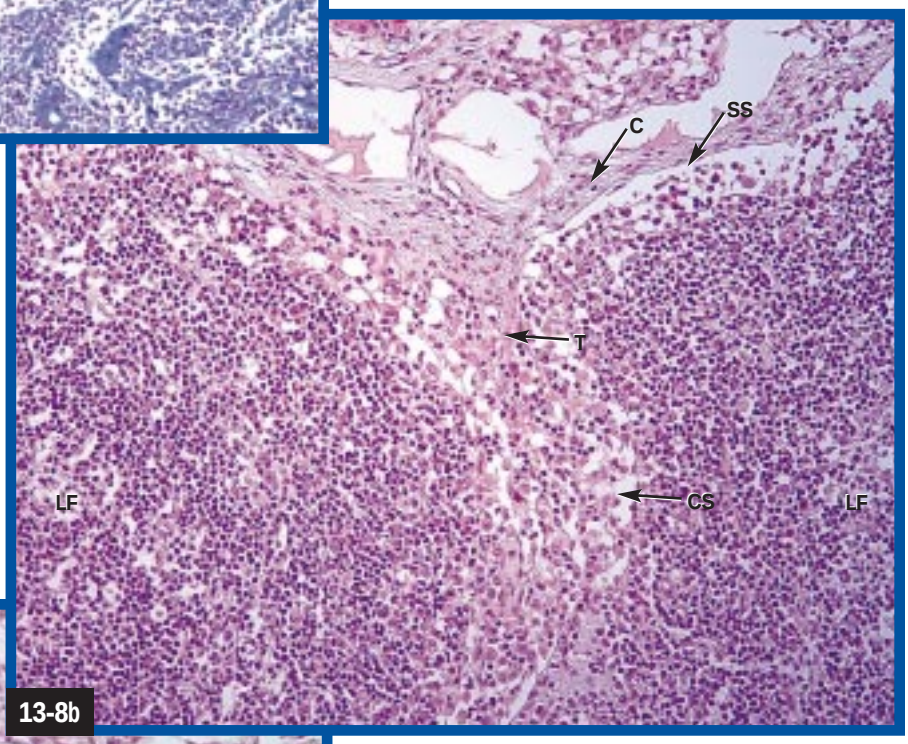

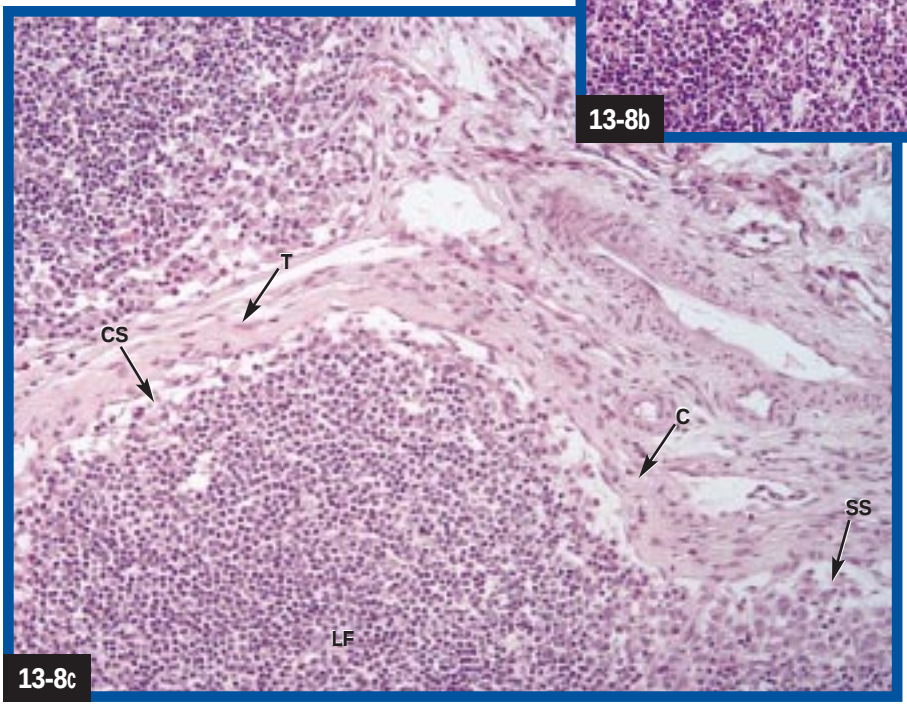

LYMPH NODE TRABECULAE AND SINUSES (a, b, and c) The interior of the lymph node is penetrated by connective tissue trabeculae (T) arising from the capsule (C). The subcapsular sinus (SS) and cortical sinuses (CS) are visible in places, but are obscured in others by lymphocytes from the lymph follicle (LF). (a is X115, b and c are X130.)

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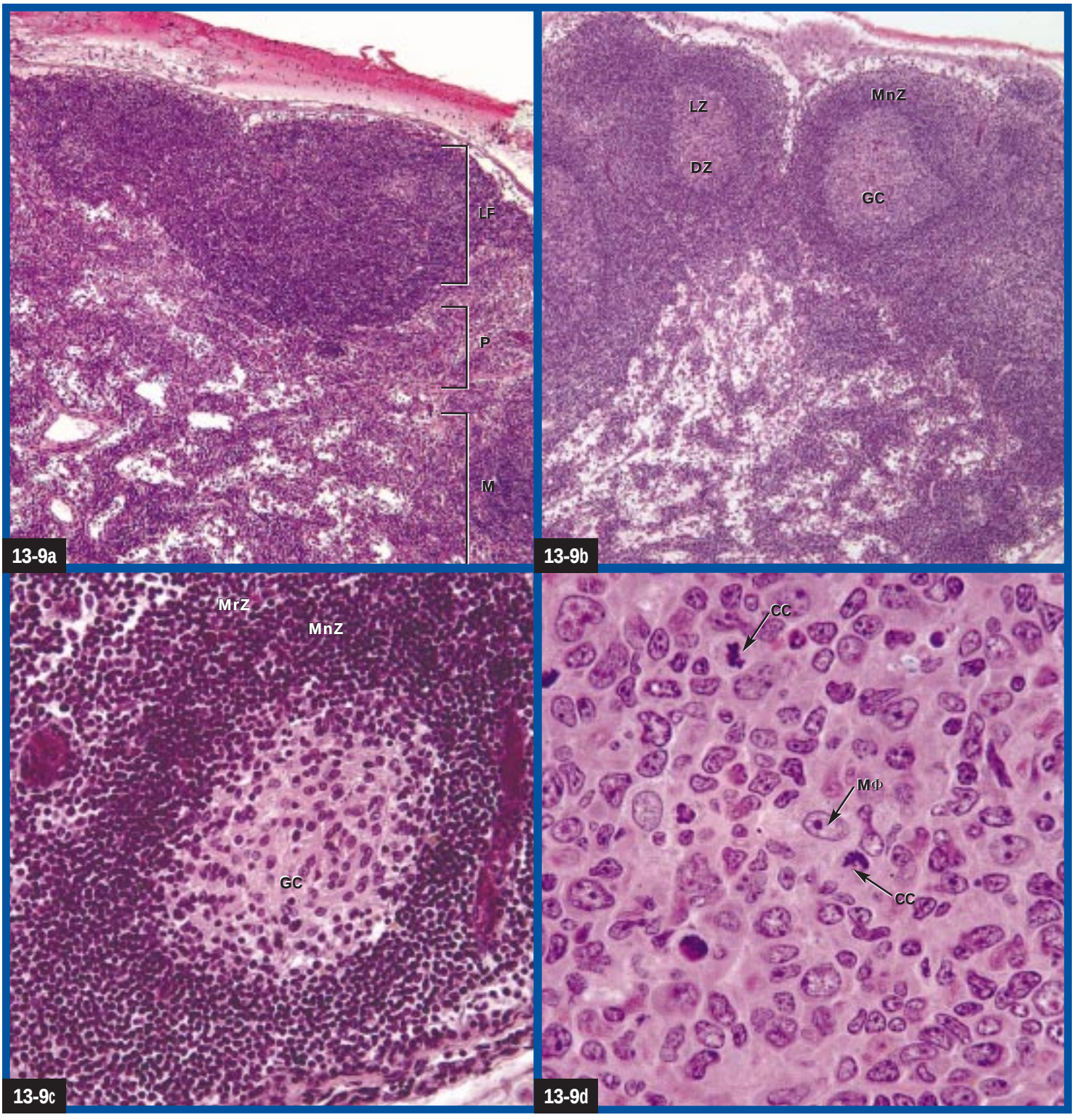

LYMPH NODE CORTEX (a) The cortex of a lymph node is composed of spherical aggregations of B lymphocytes called lymph follicles (LF). Deep to the follicles is the paracortex (P), occupied mainly by T cells. The medulla (M) is also visible. (*X65*) (b) Shown in this field are secondary follicles demonstrating the lighter germinal center (GC) and darker mantle zone (MnZ). Notice that the mantle zone is thicker on the side of the capsule and that the germinal center has a dark zone (DZ) toward the medulla and gets lighter (LZ) toward the capsule. Secondary follicles have multiplying B cells in the germinal center. (*X130*) (c) This is a secondary follicle. In addition to the germinal center and mantle zone, the lighter marginal zone (MrZ) is visible. (*X265*) (d) B cells multiply and differentiate in the germinal center, beginning in the darker portion at the medullary end and finishing at the lighter capsular end. During development, they pass through centroblast and centrocyte stages before they become plasma cells. Centroblasts are large cells with a round nucleus. These are mitotically active and produce the centrocytes. Centrocytes (CC) are recognized by their irregular nuclear membranes. Plasma cells and memory B cells are located in the light region before they migrate to the medulla. Tingible body macrophages (MΦ) are also seen. These cells phagocytose B cells that have failed to differentiate properly in response to the antigen. *(X660)*

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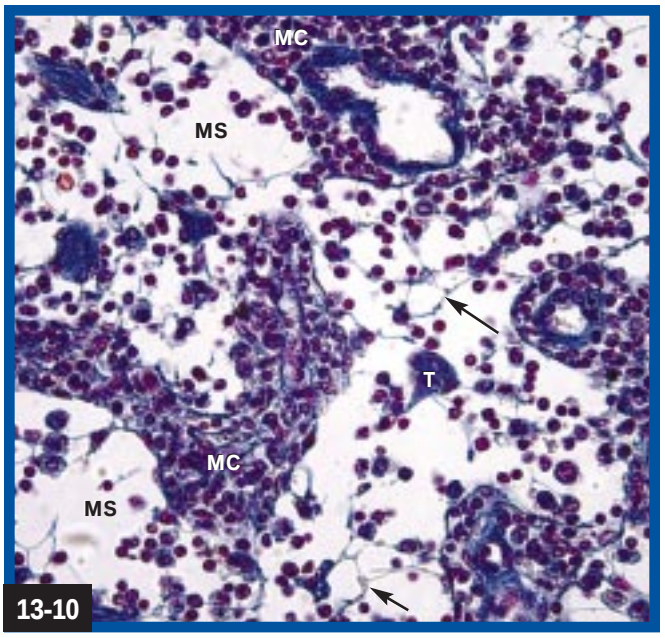
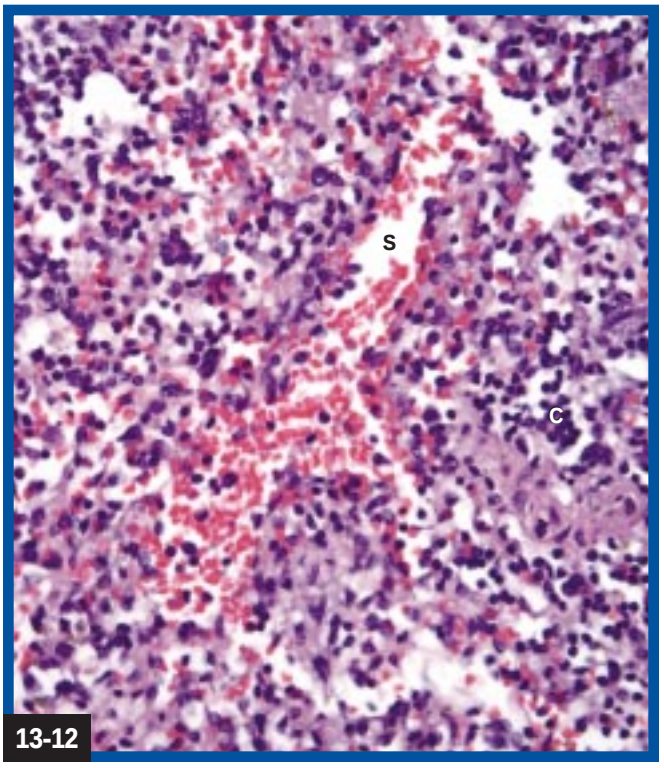
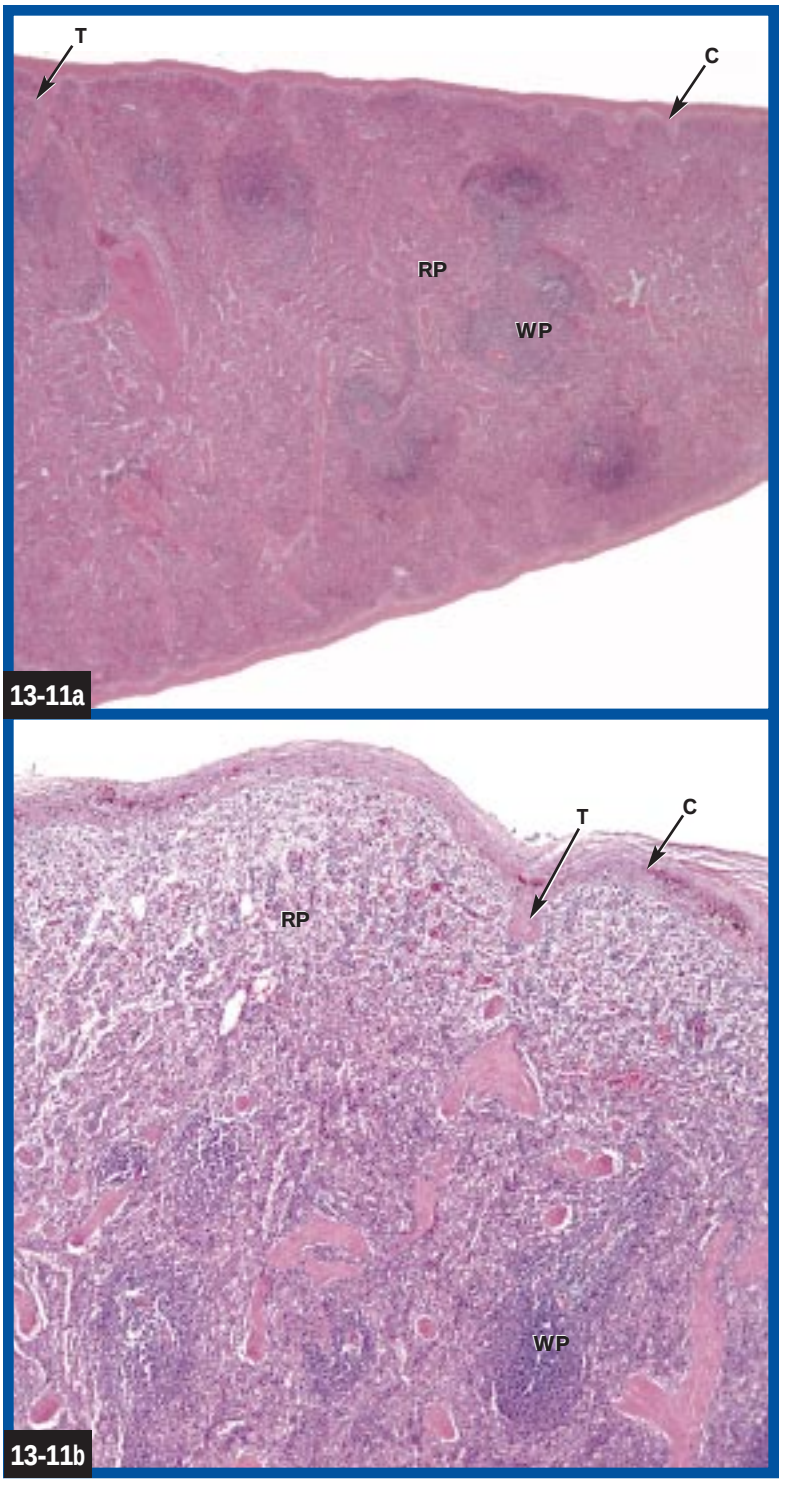


LYMPH NODE MEDULLA The lymphocytes of the medulla (mostly plasma cells) are arranged into cords (MC) and are separated by medullary sinuses (MS). The reticular connective tissue framework is visible (arrows), as are trabeculae (T).



SPLENIC RED PULP The portion of splenic parenchyma composed of blood sinuses (S), cords (C) of lymphocytes and macrophages is called red pulp due to its appearance in fresh specimens. Blood in the spleen eventually finds its way to blind capillaries surrounded by macrophages. The RBCs must pass by this macrophage layer in order to enter the red pulp. Then, they must pass through slits in the basement membrane of the sinuses, a task likely to break old, brittle RBCs. This contact with macrophages and difficult passage into the sinuses is the mechanism for removing RBCs from circulation.



SPLEEN Both micrographs show a panoramic view of the spleen with its capsule (C) and trabeculae (T). Red pulp (RP), made of blood sinuses, and white pulp (WP), made of lymphocytes, are also visible. (a) *X20* (b) *X25*

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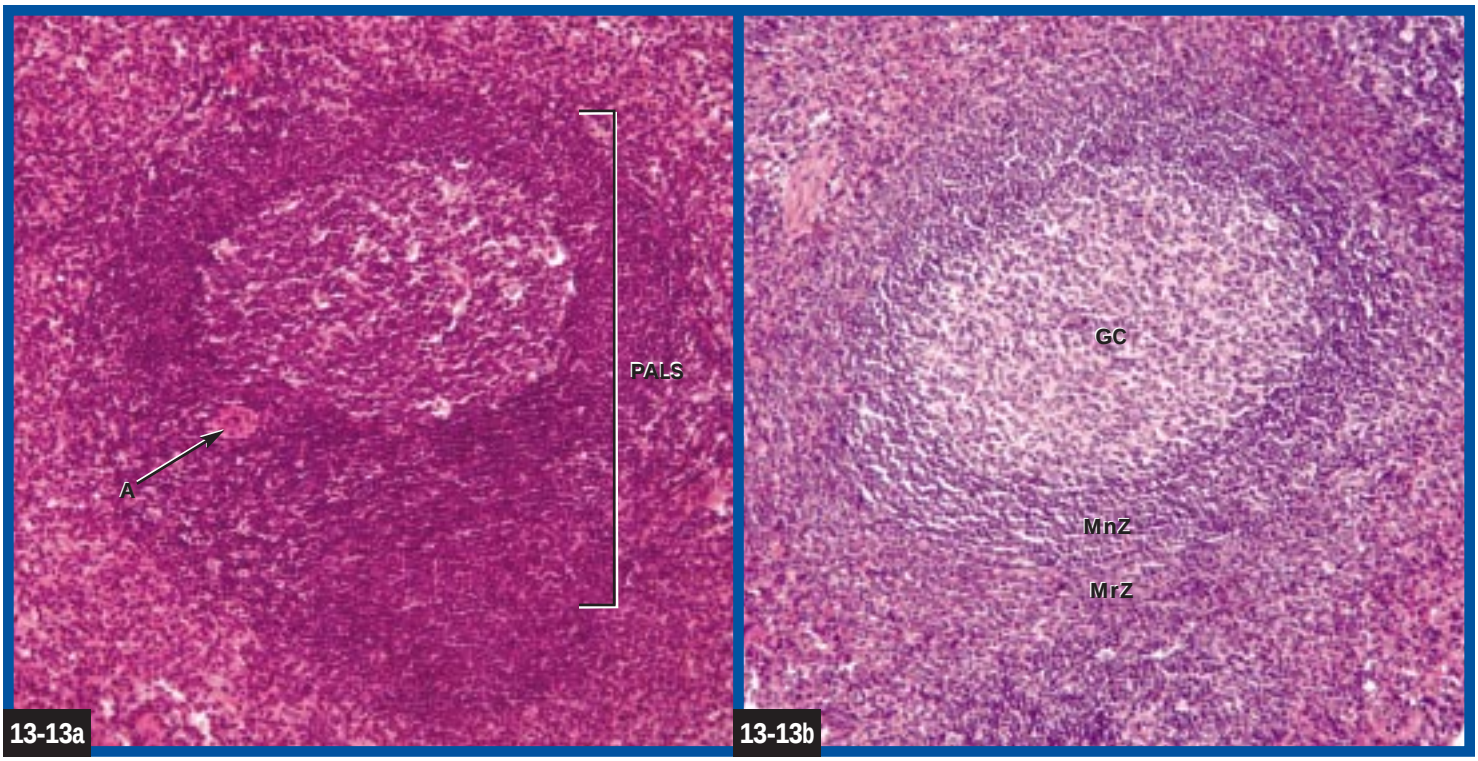
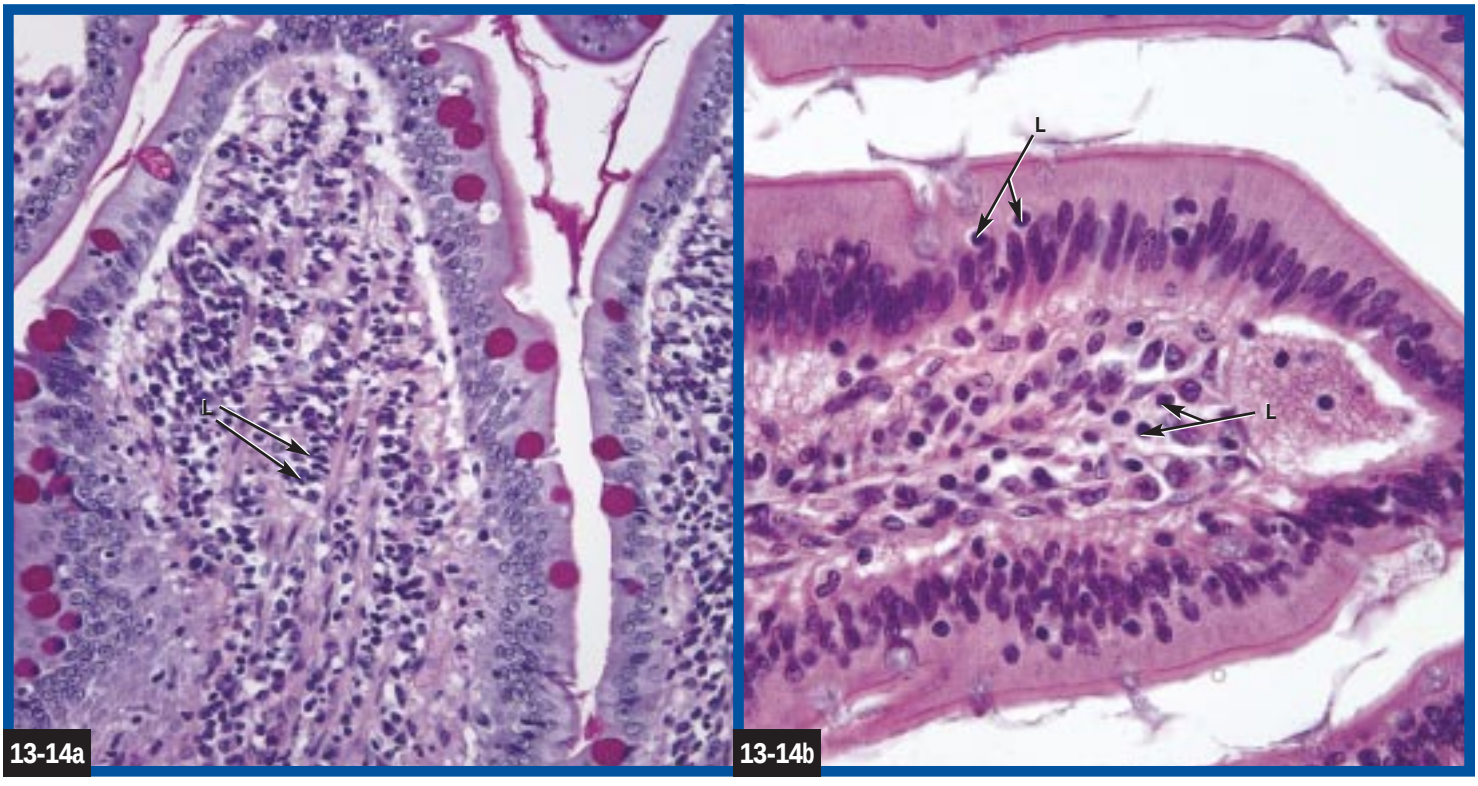


SPLENIC WHITE PULP White pulp is found in two forms. Masses of T cells form periarterial lymphatic sheaths (PALS) around arterioles (A), as in (a). B cells form follicles with a germinal center (GC), mantle zone (MnZ) and marginal zone (MrZ). These are illustrated in (b). Both micrographs are X130.



DIFFUSE LYMPHATIC TISSUE Lymphocytes are often found in the connective tissue layer of a mucous membrane and are referred to as MALT. They are characterized by small, dark staining nuclei. (a) Numerous lymphocytes (L) are visible in this preparation of small intestine mucosa. (*X250*) (b) This is another small intestine specimen. Lymphocytes are present in the connective tissue, but are also seen in the epithelium. *(X380)*

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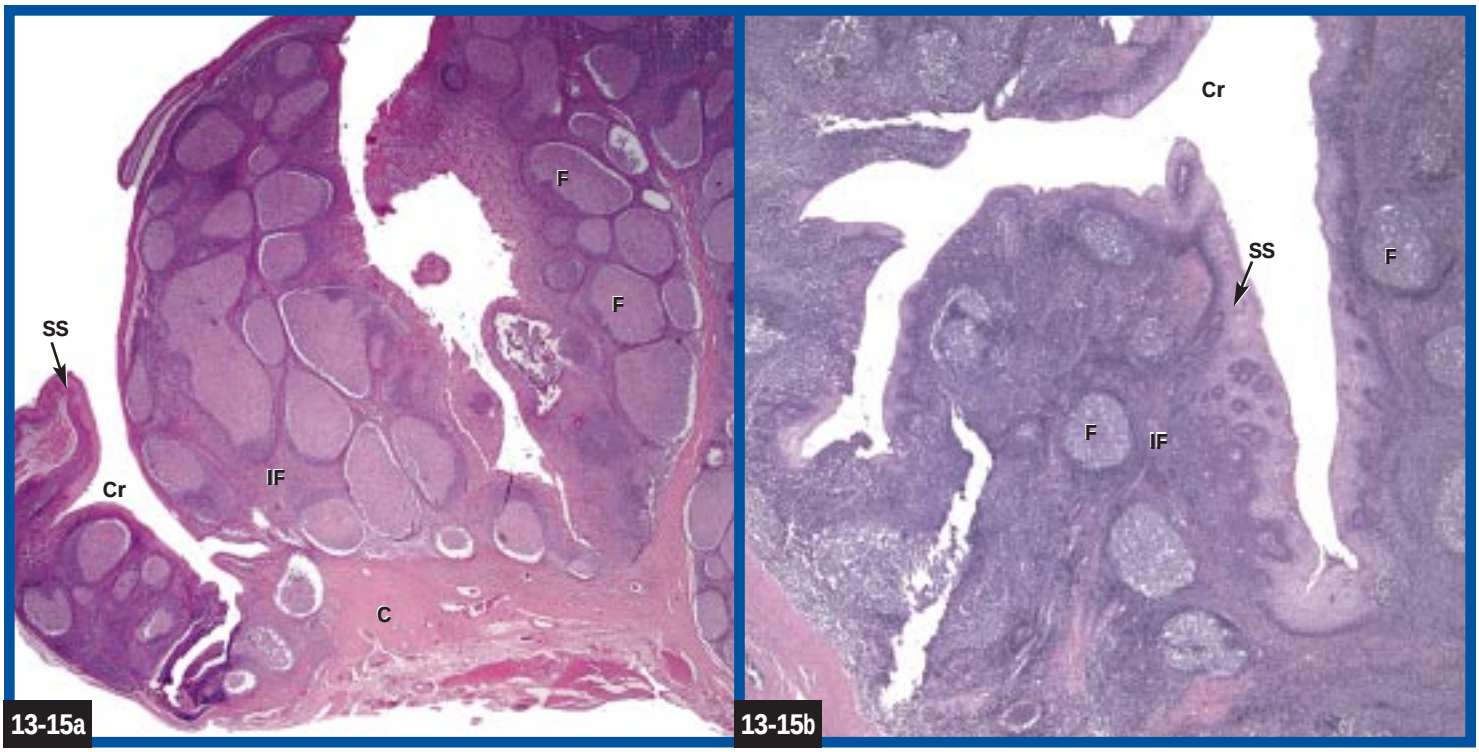
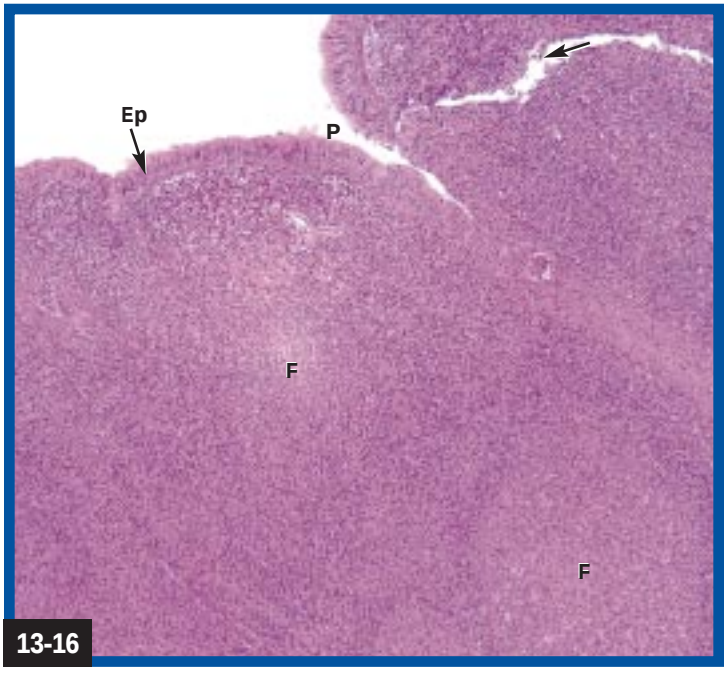
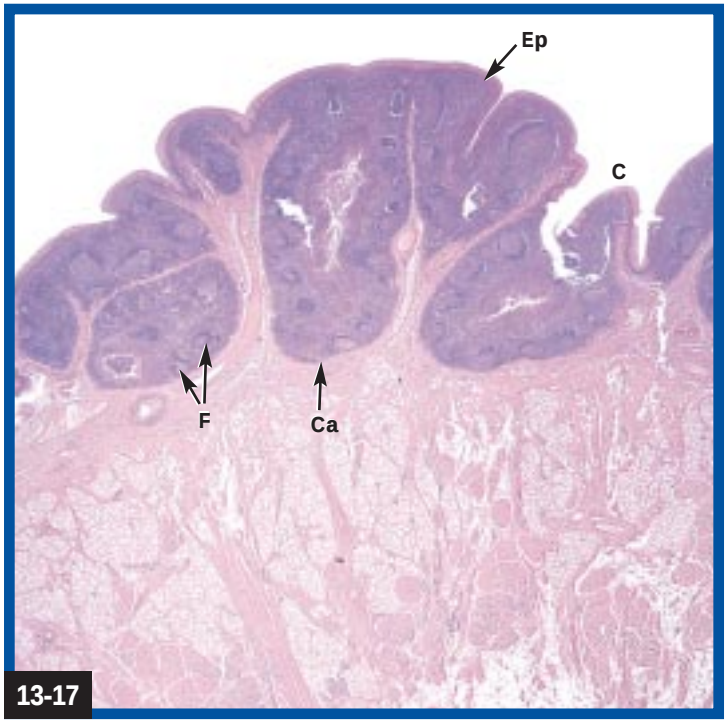


PALATINE TONSILS The palatine tonsils are covered by stratified squamous epithelium (SS) that projects down into tonsilar crypts (Cr). The bulk of the tonsil is composed of follicles with germinal centers (F), with interfollicular (IF) regions composed of T cells making up the remainder. A fibrous capsule (C) marks the lower margin of the tonsil. (a) *X8* (b) *X25*.



PHARYNGEAL TONSIL The pharyngeal tonsil is similar in construction to the palatine tonsils, but has a thinner capsule, is covered with PSCC (Ep), and has shallower depressions called pleats (P). Lymph follicles (F) are abundant. The white region indicated by the arrow is an artifact of preparation. *(X50)*



LINGUAL TONSIL Each lingual tonsil has a single crypt (C), a thin capsule at its base (Ca), and is covered with stratified squamous epithelium (Ep). Follicles (F), some with germinal centers, are also present. *(X7)*

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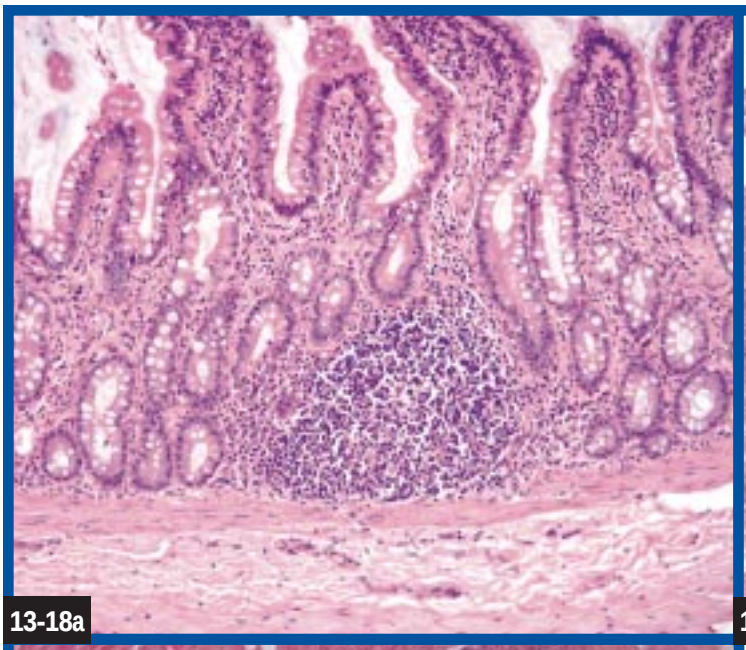
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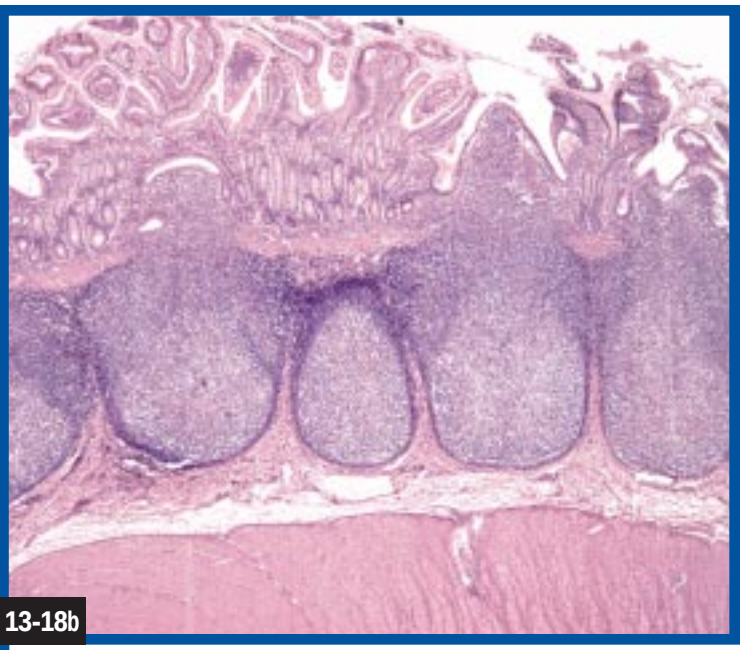
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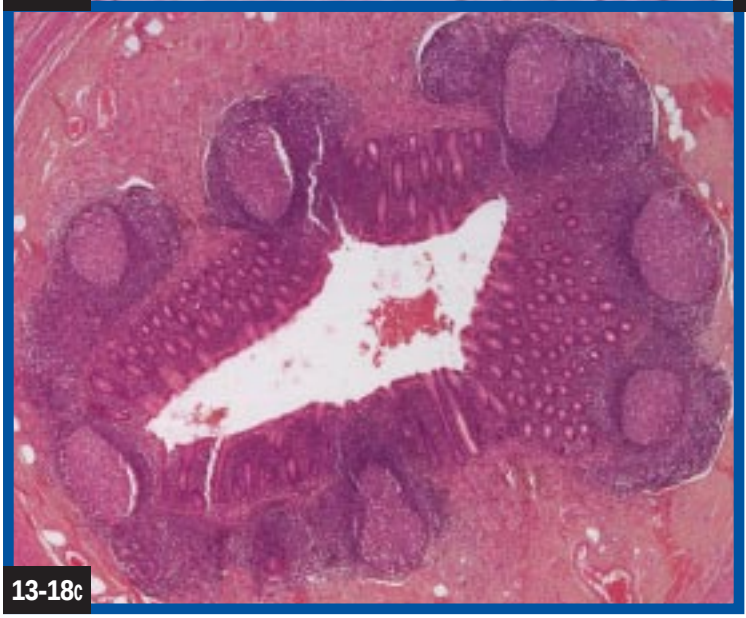
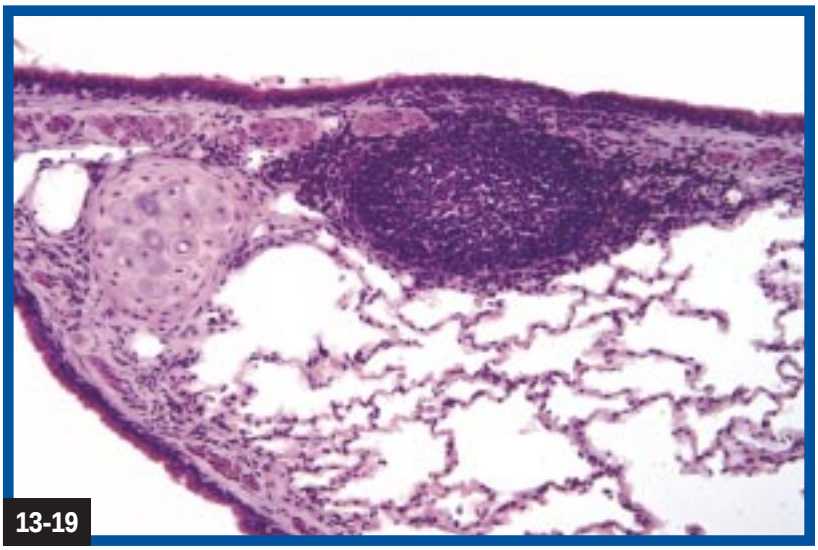

13-18c

GUT ASSOCIATED LYMPHATIC TISSUE (GALT) Lymph follicles are present in the mucosa of many digestive organs. (a) Here is a single follicle in the small intestine's mucosa. Diffuse lymphatic tissue is also present. (*X110*) (b) Aggregates of lymph follicles in the ileum are known as Peyer's patches. They are found in the submucosa. (*X25*) (c) The vermiform appendix is found on the cecum of the large intestine. It has abundant lymphatic tissue in it, as this cross section illustrates. *(X20)*


13-19

BRONCHUS ASSOCIATED LYMPHATIC TISSUE (BALT) Lymph follicles are also found associated with the respiratory tree, especially at branch points. *(X110)*

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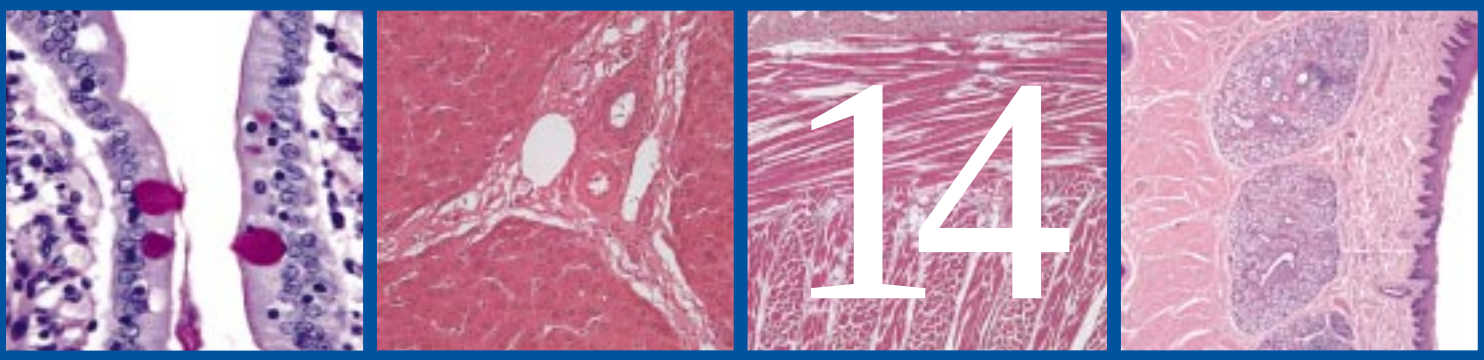
Digestive System

CHAPTER 14



Introduction to the Digestive System

The digestive system is involved in the ingestion, mechanical and chemical digestion, and absorption of food. It consists of the organs of the oral cavity (teeth and tongue), digestive tube (esophagus, stomach, small intestine, and large intestine) and accessory glands (salivary glands, liver, gall bladder, and pancreas).

Organs of the Oral Cavity

The oral cavity (Figures 14-1 and 14-2) is lined with a stratified squamous epithelium. It is nonkeratinized on the inside of the lips, cheeks, and hard and soft palates. It is partially keratinized over the gingivae (gums) and some papillae of the tongue.

Chemical digestion of starch begins in the oral cavity, but the main function is the mechanical digestion of food as it is broken up by the teeth and mixed with saliva to form a bolus.

Salivary Glands

Salivary glands (Figure 14-3) produce a secretion called saliva. Saliva is about 99% water, with mucus and the enzymes amylase and lysozyme comprising the remaining 1%. The secretory cells are arranged into acini of two types: **serous acini** and **mucous acini**. Serous acini produce a watery secretion containing enzymes and antibodies. They are typically basophilic and have a granular cytoplasm (consistent with their function of protein synthesis.) Mucous acini generally appear pale with a smooth cytoplasm and the cells' nuclei pushed toward the basement membrane. Their secretion is viscous due to the mucus in it. Occasionally, serous and mucous acini are found together, with the serous cells forming a cap over the mucous cells, a structure referred to as a **serous demilune**.

Acini empty into ducts made of secretory cells called **intercalated ducts**, which lead to larger **striated ducts**. These are lined with a simple columnar epithelium whose nuclei tend to be toward the free surface and whose cytoplasm appears striated due to numerous folds of the basal membrane. Striated ducts secrete lysozyme and antibodies (immunoglobin A).

Each acinus is associated with a flattened, contractile **myoepithelial cell** with processes that wrap around the acinus. Upon contraction, myoepithelial cells assist in moving the secretion into the duct.

There are three main salivary glands. The **parotid glands** (Figure 14-4) are located anterior to each ear and their ducts empty into the oral cavity near the second maxillary molar. A connective tissue **capsule** sends **septa** into the gland and divides it into **lobules**. Most acini are the serous type. Adipocytes become more abundant with age.

The **sublingual glands** (Figure 14-5) are located in the floor of the oral cavity. They are composed primarily of mucous acini, some with serous demilunes. Adipocytes may also be seen, especially in adults as they increase in number with age.

The **submandibular glands** (Figure 14-6) contain both serous and mucous acini, some with serous demilunes. The relatively long striated ducts make them abundant in sectioned specimens.

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Teeth

There are typically 20 **deciduous teeth** that are replaced by 32 **permanent teeth** in the adult human. There are 16 permanent teeth in each dental arch and the pattern in the mandibular and maxillary arches is the same, with two incisors, one canine, two premolars, and three molars on each side (Figure 14-7).

Each tooth (Figure 14-8) consists of a **crown** that projects above the **gingivae** or **gums**. The crown is covered with **enamel**, the hardest material in the body (95% calcium salts and 5% organic substances). Below the gumline, one or more **roots** project into **alveoli** (sockets) in the bone. The roots are covered with **cementum**, a bone-like material that lacks the Haversian systems and blood vessels of bone. The fibrous **periodontal ligament** (periodontal membrane) connects the cementum with the alveolar bone and acts as its periosteum. The **neck** of the tooth is a constriction at the junction of the crown and roots. Internally, the tooth consists of bone-like **dentin** (70% calcium salts) and a **pulp cavity** filled with the vascular loose connective tissue called **dental pulp**. The **gingiva** is a mucous membrane that covers the bone tissue of the maxilla and mandible up to the tooth's enamel. It has a keratinized stratified squamous epithelium.

Deciduous teeth develop from an invagination of thickened embryonic oral epithelium called the **dental lamina** in each jaw (Figure 14-9). The dental lamina dilates and forms an **enamel organ** for each tooth, then eventually degenerates. Deep to the enamel organ, mesenchyme begins to form the **dental papilla**. Concurrently, the enamel organ becomes cap-shaped as it grows around the papilla. Tall columnar enamel-producing **ameloblasts** begin to develop along the concave side of the enamel organ next to the papilla, then dentin producing **odontoblasts** form between the ameloblasts and the dental papilla. Further growth of the enamel organ results in a bell-shaped structure that determines the form of the particular tooth's crown. Connective tissue around the enamel organ differentiates into the **dental follicle**, the precursor of the periodontal ligament. It also forms the cementum of the root.

Odontoblasts secrete dentin between the odontoblast and ameloblast layers. As they do so, they migrate inward. A long, thin cytoplasmic process of each odontoblast remains in the dentin as the odontoblastic process, visible in light micrographs as a **dentinal tubule**. Subsequently, ameloblasts deposit enamel next to the dentin. Thus, the odontoblast and ameloblast layers become separated by the dentin and enamel each has secreted.

Tongue

The tongue (Figure 14-10) is a muscular organ covered with mucous membrane consisting of a **stratified squamous** epithelium and **lamina propria**. It possesses general sensory receptors as well as chemoreceptors for taste called taste buds. In addition, it is responsible for mixing chewed food with saliva to form a bolus. It is also involved in speech.

The surface of the tongue is covered by **papillae** of three types. **Filiform papillae** are the most numerous and are hair-like in appearance. Their epithelium is keratinized. **Fungiform papillae** are globular with a nonkeratinized stratified squamous epithelium and vascular connective tissue within, which makes them appear reddish. Six to 14 **circumvallate papillae** are located in a row in the region known as the **sulcus terminalis**, about two-thirds of the way back on the tongue. Each is surrounded by a **cleft** into which serous **von Ebner's glands** drain. Most taste buds are located in the mucosa of these papillae.

The bulk of the tongue is skeletal muscle arranged in horizontal, transverse, and longitudinal bands. These are responsible for producing the complex movements of the tongue. Filling in between the muscle and epithelial layers is a loose connective tissue lamina propria with occasional mucous and serous salivary glands.

Taste buds (Figures 9-2 and 14-10f) are light staining oval objects found in the epithelium of the oral cavity and the tongue. At the surface is the **taste pore**. Both the lighter staining **gustatory cells** and darker **sustentacular cells** are associated with neurons, but the gustatory cells are considered to be the actual chemoreceptors.

Organs of the Digestive Tube

The digestive tube consists of the esophagus, stomach, small intestine, and large intestine. The wall is divided into four main layers that show modification from one organ to another depending on function (Figure 14-11). From the lumen outward, these layers are the mucosa, submucosa, muscularis externa, and serosa or adventitia.

The **mucosa** is composed of either a stratified squamous epithelium or a simple columnar epithelium. Deep to it is a loose connective tissue layer called the **lamina propria**. In some organs, the lamina propria is displaced by glandular epithelium; in others it is occupied by numerous lymphocytes. Together, the epithelium and lamina propria form the mucous membrane of the gut. Finally, a thin layer of smooth muscle (skeletal muscle in the proximal esophagus) forms the **muscularis mucosae**.

Deep to the mucosa is the **submucosa**, a loose connective tissue that houses blood vessels, nerves, and lymphatics, as well as glands derived from the surface epithelium in some organs.

The **muscularis externa** is composed of smooth muscle in most organs, but skeletal muscle is seen in the proximal esophagus and anal canal. It is composed of an **inner circular layer** and an **outer longitudinal layer**, the coordinated contraction of which results in the propulsive movement called peristalsis.

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If the organ is in the peritoneal cavity, the outer surface is lined with a serous membrane called **visceral peritoneum**, and this constitutes the **serosa**. It is composed of a simple squamous mesothelium and a deeper fibrous connective tissue. In most parts of the gut, the serosal layer joins itself on one side of the organ and forms the double-layered mesentery that suspends the organ and carries blood vessels to and from it. If the organ is outside the peritoneal cavity, it is covered with a fibrous **adventitia** that blends in with surrounding connective tissues.

In addition to these basic layers, neural structures responsible for regulating glandular secretion and muscular contraction are present. **Meissner's plexus** is found in the submucosa and supplies the muscularis mucosae and mucosal glands. The **myenteric plexus (of Auerbach)** is located between the two muscular layers of the muscularis externa. These are aggregations of parasympathetic postganglionic neurons that supply the muscle.

Esophagus

The **esophagus** (Figure 14-12) is a muscular tube found in the mediastinum of the thoracic cavity leading from the laryngopharynx to the stomach. Peristaltic waves convey the bolus of food to the stomach. A physiological sphincter normally prevents food from being regurgitated from the stomach into the esophagus.

The relaxed esophageal mucosa is highly folded, but it flattens as the esophagus distends to accommodate the swallowed bolus. The epithelium is a nonkeratinized stratified squamous. There is a thin lamina propria and discontinuous muscularis mucosae.

The submucosa is composed of an elastic connective tissue (to accommodate swallowing) and contains serous **esophageal glands**.

Since swallowing is a voluntary action, the proximal one-third of the esophagus contains skeletal muscle in the muscularis externa and muscularis mucosae. By the distal one-third of the esophagus, the muscle layers are made exclusively of smooth muscle. The muscularis externa is thick and has well-defined layers.

All but the distal centimeter of the esophagus is located in the mediastinum and as such is covered by a fibrous adventitia. The terminal part of the esophagus, which has passed through the diaphragm to join the stomach, is lined with a serosa.

Stomach

The stomach is a dilation of the digestive tube that becomes further distended as food is stored in it. Internally, the mucosa of an empty stomach is thrown into nonpermanent longitudinal folds called **rugae** (Figure 14-13). As the stomach fills, the rugae flatten to accommodate the increased volume. In addition to storage, the stomach is involved in chemical digestion of proteins and further mechanical digestion of the food to make chyme.

The stomach is divided into four regions. The esophagus enters at the **cardia**. Superior to this is the **fundus**. The main portion is called the **body** or **corpus**, and the end joining the small intestine is the **pyloris**.

The mucosa of the esophagus changes abruptly as it joins the cardia (Figure 14-14). At the **esophageal-cardiac junction**, the stratified squamous becomes a simple columnar epithelium, and the lamina propria becomes occupied by gastric glands (see below). All other layers are continuous across the junction.

The mucosa of the stomach (Figure 14-15) has depressions called **gastric pits**. Leading from each pit is an **isthmus** which gives rise to tubular **gastric glands**. With the light microscope, three cell types are identifiable. These are the chief cells, mucous cells, and parietal cells.

Mucous cells are found on the luminal surface and line the pits. They are also in the necks of the glands. These mucous cells can be differentiated from the surface mucous cells using the electron microscope. The mucus produced coats the stomach lining and protects it from the low pH and enzymes of gastric juice.

Parietal cells are eosinophilic and appear reddish with H&E stains. They secrete hydrochloric acid and intrinsic factor (necessary for absorption of Vitamin B_{12}). They are most abundant in the isthmus region, but may be found throughout the gland.

Chief (zymogenic) cells are distributed throughout the gland, but are most abundant near the base. These cells are basophilic and their granular cytoplasm appears purplish with H&E stains. They secrete the precursor to the enzyme pepsin.

There is regional variation in the gastric mucosa (Figure 14-16). Deep pits and an abundance of mucous cells in the glands characterize the cardiac region. The fundus and body, which comprise the majority of the stomach, have shallow pits and typical gastric glands composed of mucous, parietal, and chief cells. The pyloric region has deep pits penetrating to about half the thickness of the mucosa. Mucus cells are abundant in the glands.

The stomach's submucosa is not remarkable, but the muscularis externa has an additional innermost oblique layer. At the pyloric-duodenal junction, the circular layer thickens to form the pyloric sphincter. The outer surface is covered with a serosa.

Small Intestine

The **small intestine** is approximately 3 meters in length. It begins at the duodenum (25 cm long) and continues as the jejunum (1 m long), and ends with the ileum (2 m long). Each segment has characteristic features (see next page). It is anchored to the dorsal body wall by a fan-shaped mesentery that supplies blood vessels, nerves, and lymphatics.

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Chemical digestion of chyme continues in the small intestine as it is mixed with enzymes in pancreatic juice and secretions of the intestinal mucosa. It is also the primary site of nutrient absorption into the blood. Consistent with its absorptive function, the mucosa is modified to increase surface area (to an amazing 600m^2!). On a gross level, **plicae circulares** (Figure 14-17) are permanent mucosal folds that are visible to the naked eye. Extending from the mucosal surface are the finger-like **villi** that are just barely visible to the naked eye. These give the internal surface an appearance of velvet. Lastly, each epithelial cell has microscopic **microvilli** extending from its surface, visible with the light microscope as a **brush border**.

The intestinal mucosa (Figure 14-18) is lined by a simple columnar epithelium with a brush border and mucous secreting goblet cells. Villi project out of the mucosa and increase its surface area. Between villi are **intervillous spaces**. **Intestinal crypts (of Lieberkühn)** are depressions into the mucosa between the villi. The space within a crypt is very small compared to the intervillous space. Further, the crypts often appear as ovals lined with epithelium that are disconnected with the surface due to the plane of section. Crypts produce an alkaline fluid and act as a source of new epithelial cells to replace old, worn out ones. **Paneth cells**, which produce antimicrobial substances, may be seen deep in the crypts. They possess eosinophilic granules near their apices.

The lamina propria within each villus has a capillary bed, a lymphatic lacteal (capillary), and an abundance of scattered lymphocytes.

Brünner's glands in the submucosa characterize the duodenum (Figure 14-19). They empty their alkaline, mucoid secretion into the duodenal lumen via the crypts where it counteracts the acidity of the chyme entering from the stomach. The cells have a typical mucous-secreting cell look. That is, they are pale staining with a flattened nucleus near the base.

Other than villus shape (that is difficult to determine in most preparations), the jejunum has no microscopic features that differentiate it from the duodenum and ileum (Figure 14-20). In most instances, it must be identified by the absence of the features seen in the other parts.

The ileum (Figure 14-21) is characterized by **Peyer's patches,** aggregations of several dozen lymph follicles in the submucosa on the side of the intestine opposite the mesentery. Whereas isolated lymph follicles are visible in all parts of the small intestine, only the ileum has them in this great a quantity.

The small intestine's muscularis externa is smooth muscle and the circular and longitudinal layers are well-defined. A serosa lines the outer surface, except for the posterior of the duodenum, which is retroperitoneal.

Large Intestine

The **large intestine** is divided into a **cecum**, **ascending colon**, **transverse colon**, **descending colon**, and **rectum**. Its primary function is to absorb water from the undigested, unabsorbed material entering from the small intestine. The large intestine begins at the **ileocecal junction** and the ileocecal valve prevents backflow of material into the small intestine.

Nonpermanent folds of the colon's mucosa may be present, but there are no villi (Figure 14-22). The epithelium is a simple columnar with abundant goblet cells. Straight **crypts of Lieberkühn** extend down to the muscularis mucosae. These are involved in absorption of water and production of new cells by mitosis. Lymphatic follicles and diffuse lymphatic tissue may be seen in the lamina propria.

The muscularis mucosae is usually prominent. The inner circular muscle layer is unremarkable, but the outer longitudinal layer is modified to form three bands called **taenia coli muscles** (Figure 14-23). The surface is covered with serosa, except for parts of the ascending and descending colon.

The **rectum** is the straight, terminal portion of the large intestine. Its mucosa resembles the rest of the large intestine, but the crypts are shallower and the goblet cells are more abundant. At the **rectoanal junction** (Figure 14-24), the simple columnar epithelium abruptly changes back to a stratified squamous. Thickening of the circular muscularis externa forms the **internal anal sphincter**. A ring of skeletal muscle outside the muscularis externa forms the **external anal sphincter**.

The **appendix** (Figure 13-18c) is a short tubular structure arising from the cecum. Its mucosa resembles the rest of the large intestine, but there is an abundance of lymphocytes in the lamina propria and the submucosa.

Glands of the Digestive Tract

The liver, pancreas, and gall bladder are derived as outgrowths of the embryonic digestive tube and they retain their connection with the gut's lumen in the postnatal individual.

Liver

The **liver** is located inferior to the diaphragm in the upper right abdominal quadrant and is the largest internal organ of the body. It is divided into four lobes, which are further divided into microscopic **lobules** (Figures 14-25 and 14-26). Traditionally, lobules have been considered the structural and functional units of the liver, but other interpretations also have merit. This being a histology book and not a physiology book, the traditional view will be presented.

The hepatic artery and the hepatic portal vein provide two sources of blood to the liver. The former supplies

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oxygen-rich blood, whereas the latter brings nutrient-rich blood from the digestive organs to be processed by the **hepatocytes**, the cells of the liver.

The liver performs a variety of functions, including detoxification of chemicals, phagocytosis of worn out RBCs, synthesis of plasma proteins and plasma lipoproteins, glucose metabolism (starch storage and gluconeogenesis), storage of certain vitamins, and production of bile.

All liver functions are performed by the hepatocytes, and most of them require close contact with the blood. As such, the hepatocytes are arranged in **plates** or **cords** of cells separated by large capillaries called **sinusoids**. The cords are usually a single cell thick, and the sinusoids are lined with endothelial cells and phagocytic **Kupffer cells**. Blood from branches of the hepatic artery and hepatic portal vein enters the sinusoids at several points along the periphery of the lobule. As blood flows by the hepatocytes, they remove and deposit whatever nutrients are appropriate. The blood is drained from the lobule by a **central vein**, which ultimately leads to the hepatic vein.

Small intercellular channels called **bile canaliculi** (Figure 14-27) carry bile produced by the hepatocytes. The canaliculi only exist as separations between cells; they are not tubes apart from the cells. Bile flows through the canaliculi toward the periphery of the lobule and empties into a **bile duct**. Bile ducts converge and ultimately lead to hepatic ducts that emerge from the liver.

The system of bile ducts and the branches of the hepatic artery and hepatic portal vein travel together within the liver and constitute a **hepatic (portal) triad** (Figure 14-28). Note that flow of materials within the triad's components is in opposite directions; blood is coming in and bile is flowing out.

Gall Bladder

The **gall bladder** (Figure 14-29) is a small, blind sac found inferior to the liver. It receives bile from the **common hepatic duct** via the **cystic duct**. Once in the gall bladder, bile is concentrated and stored until it is needed. Contraction of the gall bladder ejects bile back out the cystic duct, into the **common bile duct** and into the duodenum. Bile is alkaline and assists in neutralizing the acidic chyme entering the duodenum from the stomach. It also is important in lipid digestion as it emulsify fats.

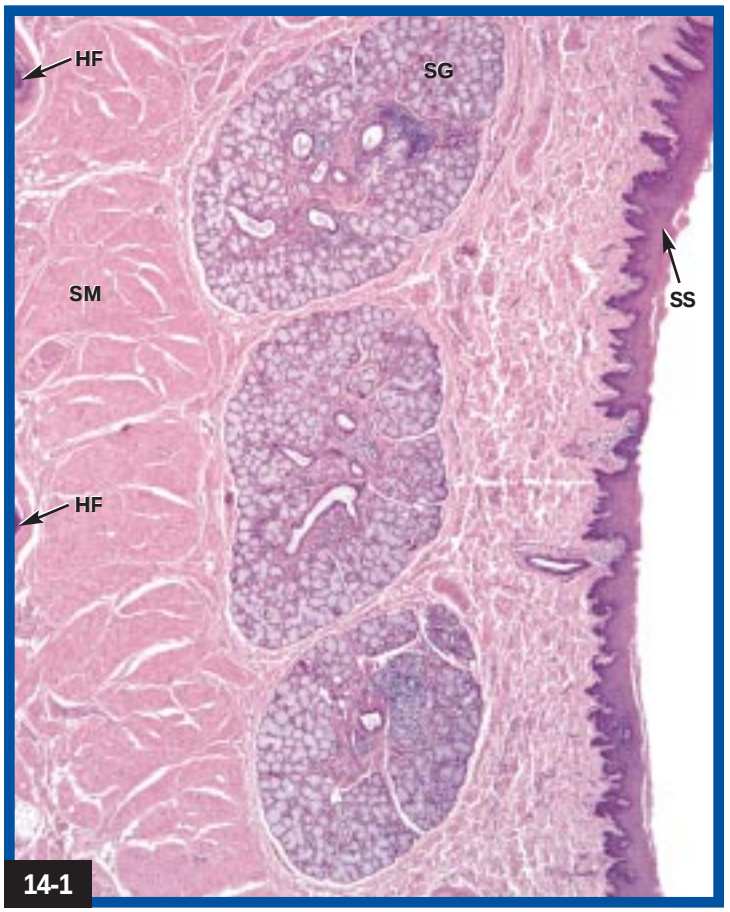
The mucosa is folded into **rugae**. A simple columnar epithelium that is active in absorbing water and electrolytes to concentrate the bile lines it. There is no muscularis mucosae or submucosa. The **muscularis** is made of indistinct layers.

Pancreas

The **pancreas** has both endocrine (Chapter 10) and exocrine components. It is the latter that we are concerned with here. Pancreatic juice is alkaline, contains over 20 enzymes, and is delivered to the duodenum by the **pancreatic duct**.

The pancreas (Figures 14-30 and 14-31) has a thin fibrous **capsule** that sends septa into the gland to divide it into **lobules**. The exocrine component is composed of numerous secretory **acini**. The cells are roughly triangular and have a granular cytoplasm typical of zymogenic (enzyme secreting) cells. That is, they have a basophilic cytoplasm due to the extensive rough endoplasmic reticulum. They also have eosinophilic zymogen granules at their apex. There are no myoepithelial cells associated with the acini.

Each acinus empties its pancreatic juice into **intercalated ducts** made of **centroacinar cells**, which are unique in beginning within the acinus. Intercalated ducts empty into **intralobar ducts** and then into **interlobar ducts** in the gland's septa. Ultimately, pancreatic juice is delivered to the duodenum by the main and accessory pancreatic ducts. The main pancreatic duct joins the common bile duct in the wall of the duodenum as the **ampulla of Vater** (Figure 14-32).



LIP Shown is the posterior of the lip. The oral mucosa is lined with nonkeratinized stratified squamous (SS). Also present are accessory salivary glands (SG) and skeletal muscle (SM). Barely visible at the left are portions of two hair follicles (HF). *(X25)*

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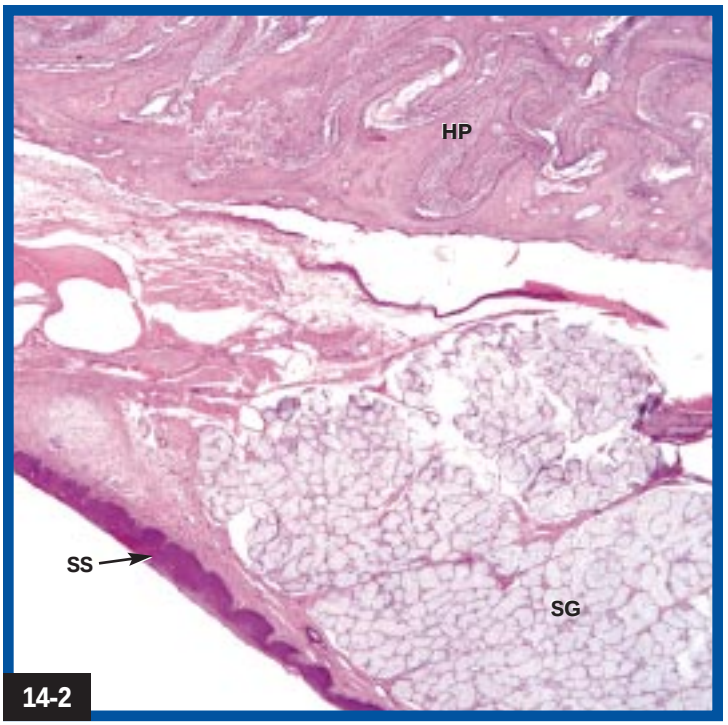
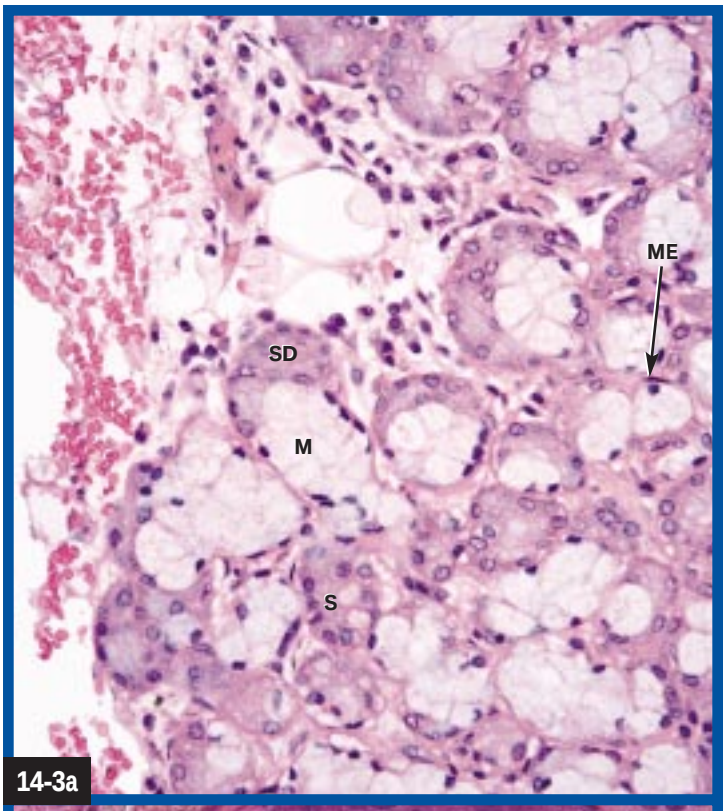
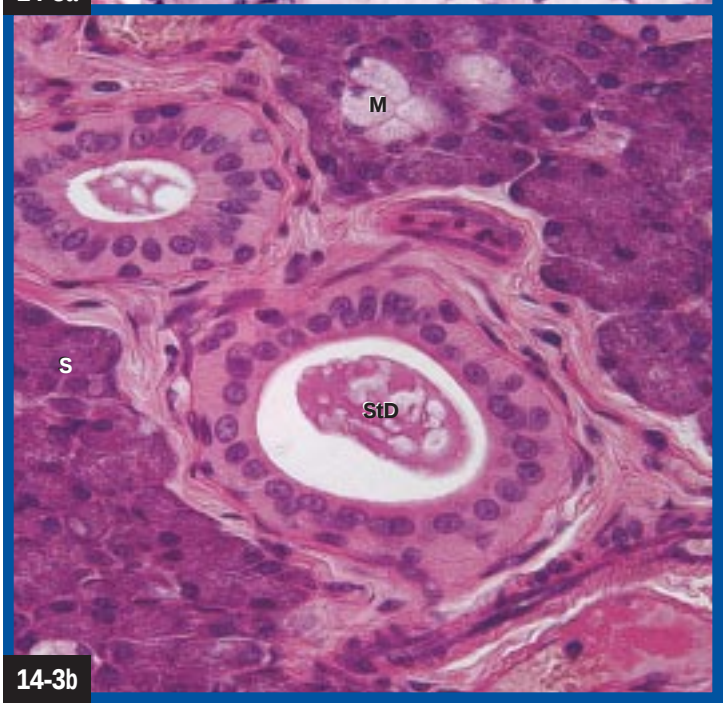


SOFT PALATE The soft palate is lined with a nonkeratinized stratified squamous epithelium (SS). Also visible are accessory salivary glands (SG) and the maxillary bone of the hard palate (HP). *(X25)*





BASIC COMPONENTS OF A SALIVARY GLAND Salivary glands have secretory mucous acini (M) and serous acini (S). The cells of mucous acini tend to be light staining with the nuclei pushed toward the basement membrane. They secrete mucus. Cells of serous acini tend to be darker staining (basophilic) and granular, an appearance typical of enzyme secreting cells. On occasion, serous demilunes (SD) form over a mucous acinus. Myoepithelial cells (ME) wrap around the acini and assist in moving the secretion out the ducts. Striated ducts (StD) are lined with a simple columnar epithelium. The nuclei are toward the apical edge and the basal cytoplasm is vertically striated. (a) This specimen is from the sublingual gland. (*X265*) (b) This specimen is from the submandibular gland. *(X400)*

PAROTID GLAND The parotid gland is made predominantly of dark staining serous acini (S). A few adipocytes (A) and a couple of striated ducts (StD) are also visible. *(X265)*

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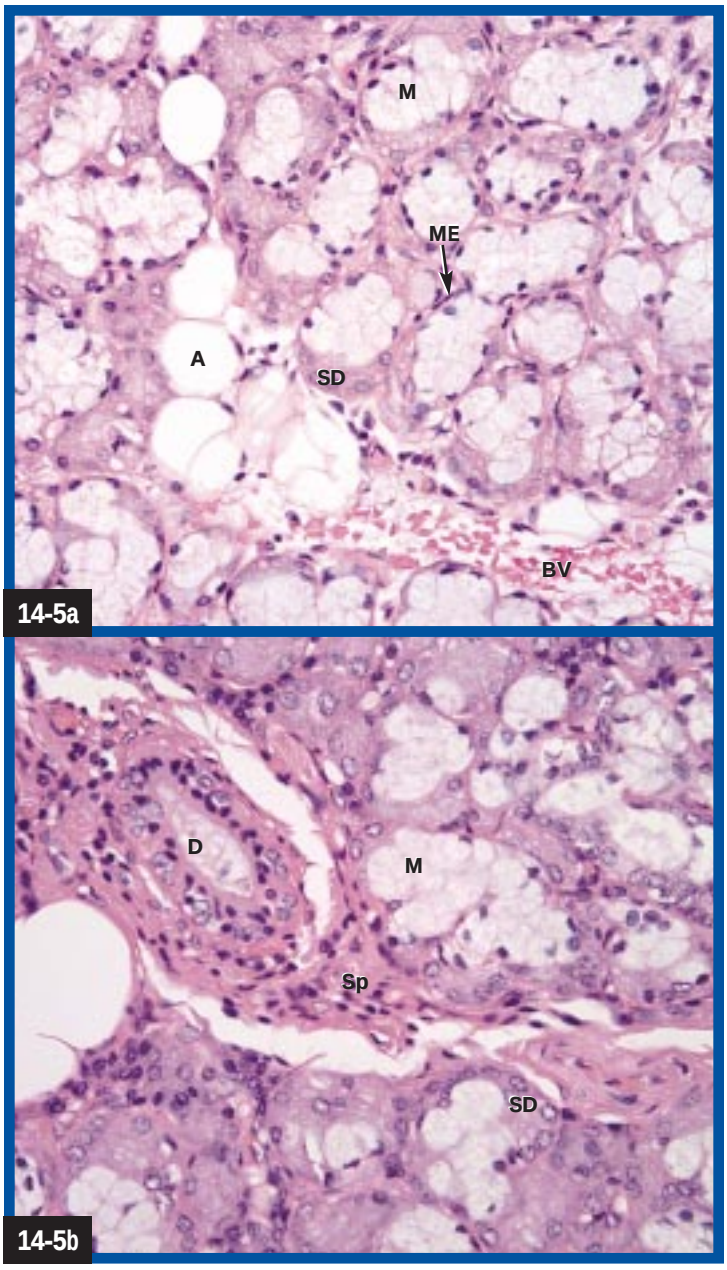
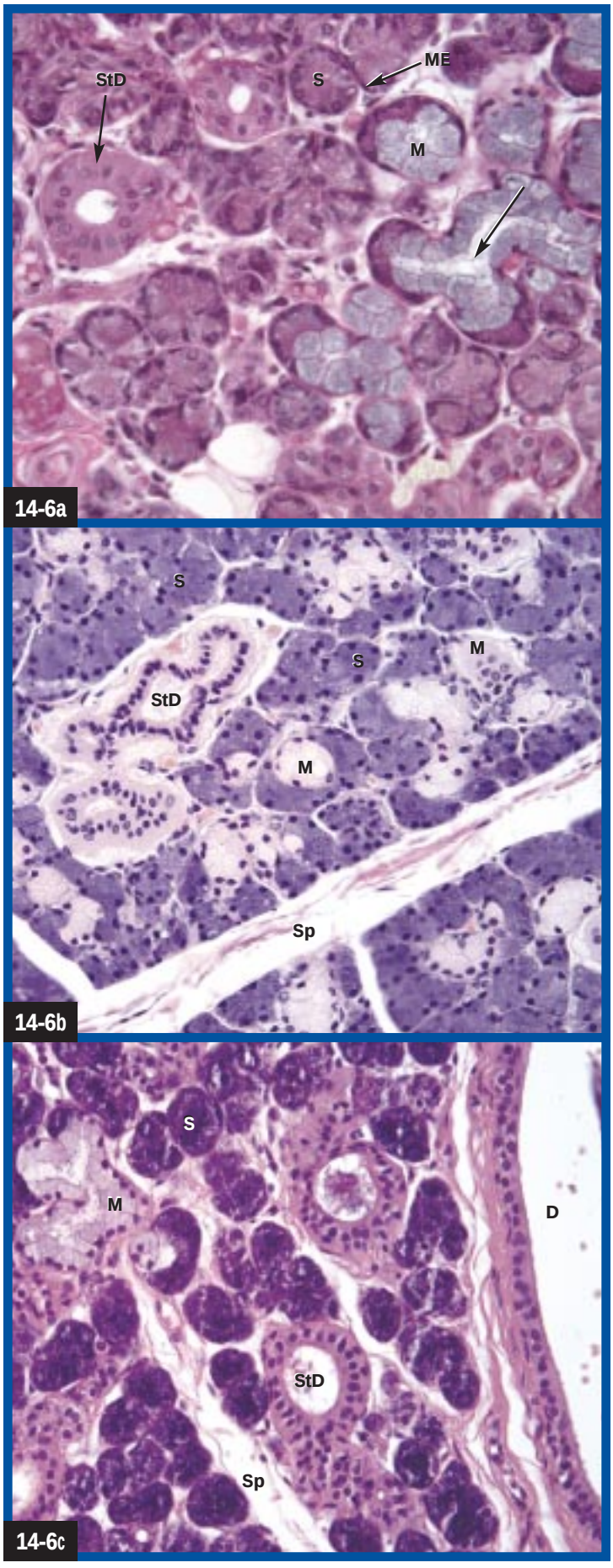


SUBLINGUAL GLAND The sublingual gland consists mostly of mucous acini (M), some with serous demilunes (SD). (a) In addition to the acini, myoepithelial cells (ME) and adipocytes (A) are visible in this specimen, as is a blood vessel (BV). (*X230*) (b) A duct (D) is seen in a connective tissue septum (Sp) in this specimen. *(X265)*



SUBMANDIBULAR GLAND The submandibular gland is a tubuloacinar gland, with the serous components (S) outnumbering the mucous components (M). The mucous cells are often in a tubular arrangement. Striated ducts (StD), myoepithelial cells (ME) and connective tissue septa (Sp) are also present. (a) In this specimen, the tubular arrangement of mucous cells is clearly seen (arrow). (*X265*) (b) The lobed nature of the submandibular gland is visible in this preparation. (*X210*) (c) A major duct is visible in this specimen (D). It is lined with a stratified columnar epithelium. *(X230)*

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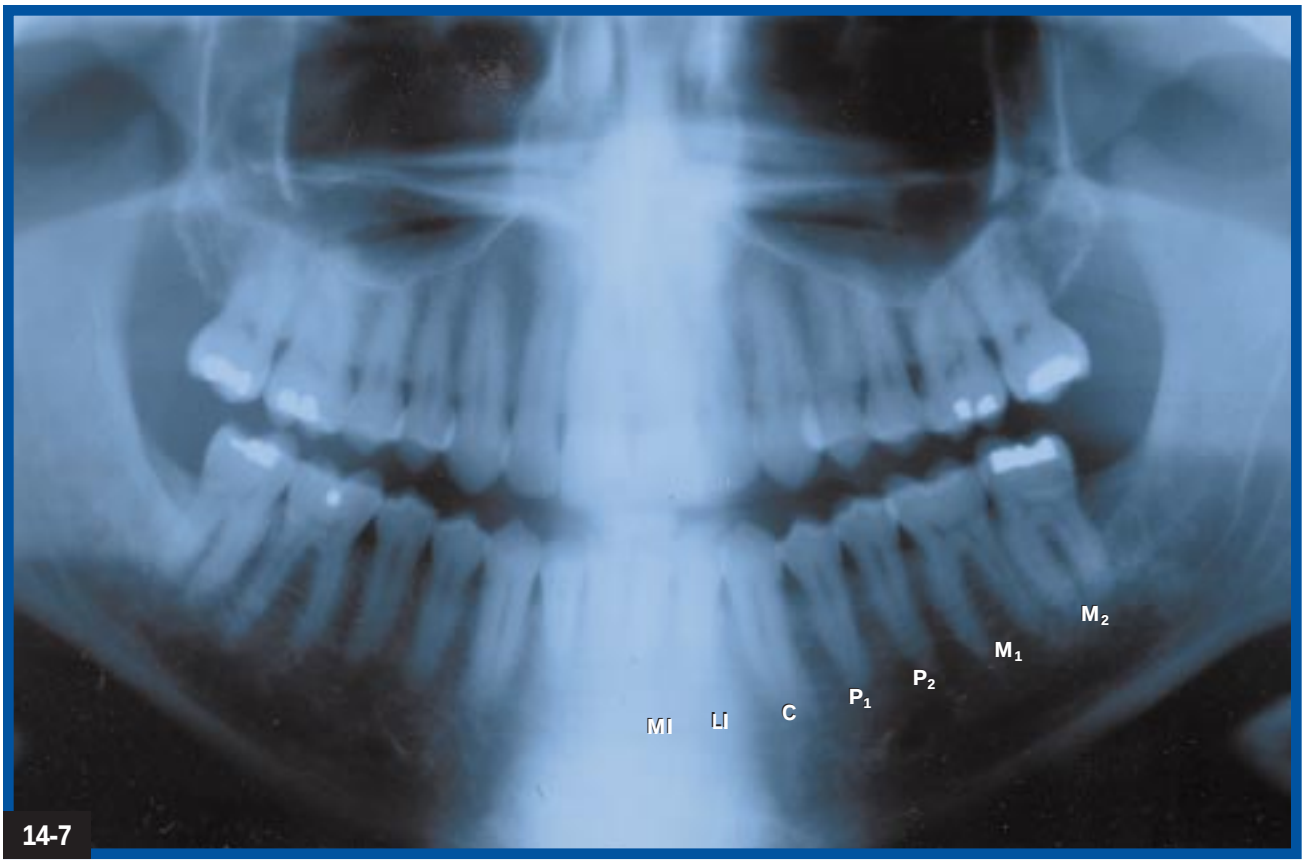
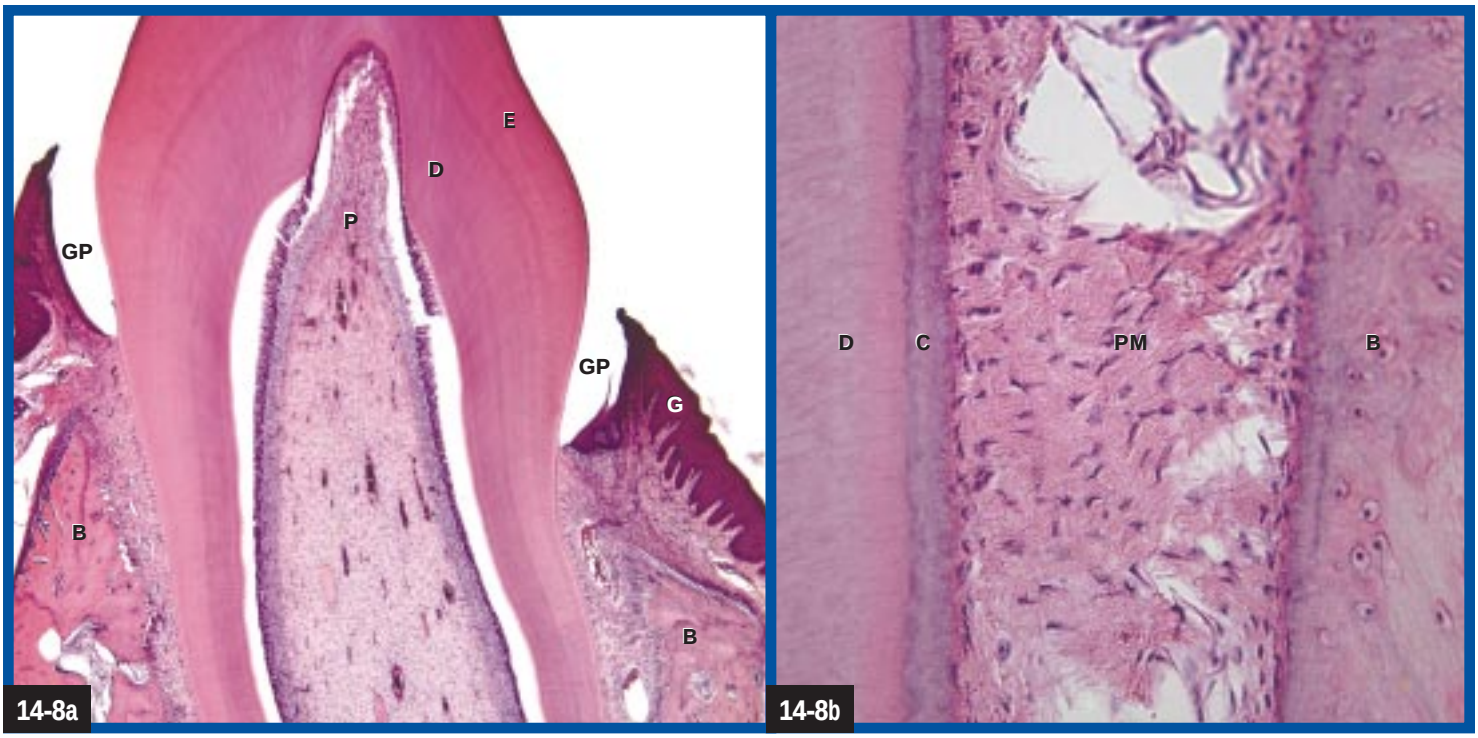


THE ADULT DENTITION Shown is a radiograph of maxillary (upper) and mandibular (lower) dental arches. Starting from the center of each arch are the medial (MI) and lateral incisors (LI), the canine (C), the first (P_1) and second premolars (P_2), and the first (M_1), second (M_2), and third molars. Note: the third molars of each dental arch are the wisdom teeth and they have been removed from this patient. (Radiograph courtesy of Paul C. Howard, D.M.D.)



TOOTH (a) In this section of a tooth, dentin (D), enamel (E), pulp (P), gingivae (G), gingival pocket (GP), and alveolar bone (B) are visible. *(X25)* (b) This is a high power magnification of the tooth root. The periodontal membrane (PM) made of collagen fibers (Sharpey's fibers) binds the tooth to the bony alveolus (B). Cementum (C) and dentin (D) are also visible. *(X380)*

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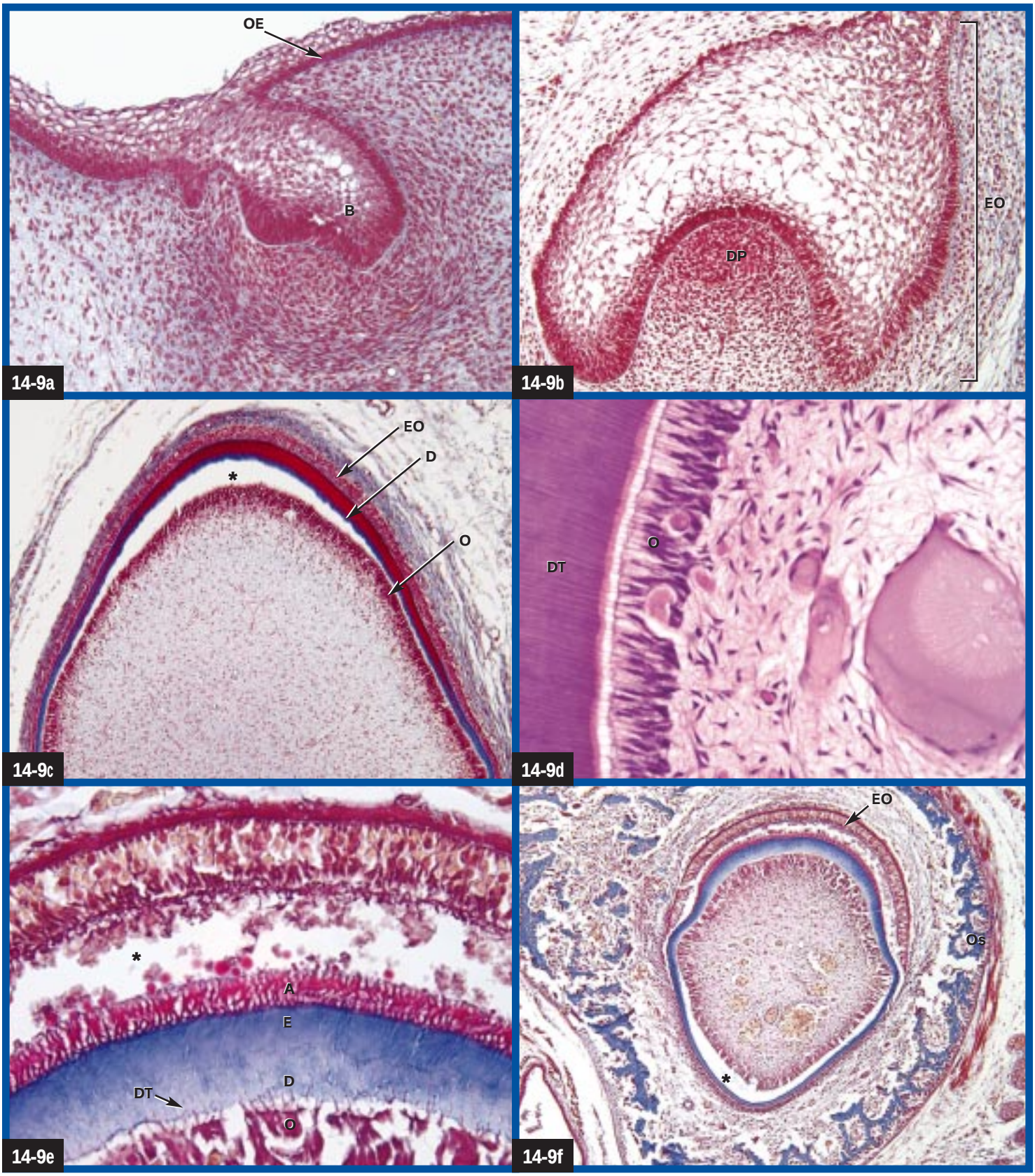

TOOTH DEVELOPMENT (a) The dental lamina has dilated to form a bud, the first evidence of an enamel organ. (*X130*) (b) The cap stage is characterized by the formation of a dental papilla, which becomes surrounded by the developing enamel organ. (*X110*) (c) In this much later stage, the enamel organ is fully formed. (*X65*) (d) This micrograph shows dentin formation. (*X250*) (e) This micrograph shows the ameloblast layer enamel. It also shows dentin formation. (*X365*) (f) This is a cross section of a developing tooth. (*X60*) Key to symbols used: **DL** = dental lamina, **B** = bud, **OE** = oral epithelium, **DP** = dental papilla, **D** = dentin, **E** = enamel, **EO** = enamel organ, **O** = odontoblasts, **DT** = dentinal tubules, **A** = ameloblasts, **Os** = bone, ***** = artifactual space.

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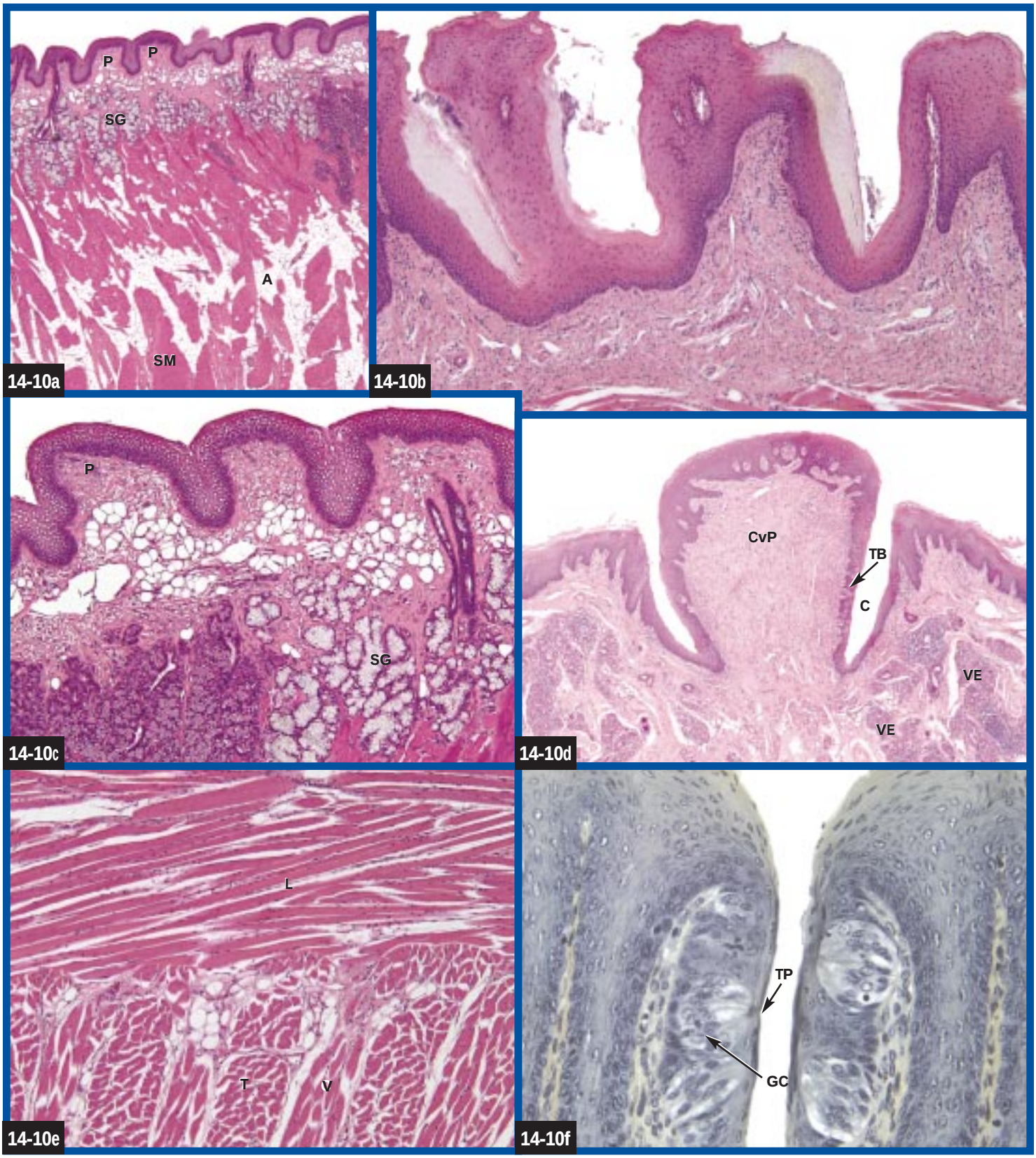

TONGUE (a) In this panoramic view of the tongue, lingual papillae (P) are seen as projections from the surface. Skeletal muscle (SM), adipose tissue (A), and accessory salivary glands (SG) are also visible. (*X20*) (b) Filiform papillae are the most numerous of papillae and are lined with a keratinized stratified squamous epithelium. (*X50*) (c) These fungiform papillae are lined with a nonkeratinized stratified squamous epithelium. (*X65*) (d) Circumvallate papillae (CvP) have the greatest density of taste buds (TB) in their nonkeratinized stratified squamous epithelium. Serous von Ebner's glands (VE) are seen in the lamina propria and empty into the cleft (C) around the papilla. (*X25*) (e) Skeletal muscle in the tongue is arranged vertically (V), longitudinally (L), and transversely (T), all of which are seen in this specimen. (*X60*) (f) These taste buds (TB) are in fungiform papillae. A taste pore (TP) and gustatory cells (GC) are visible. *(X250)*

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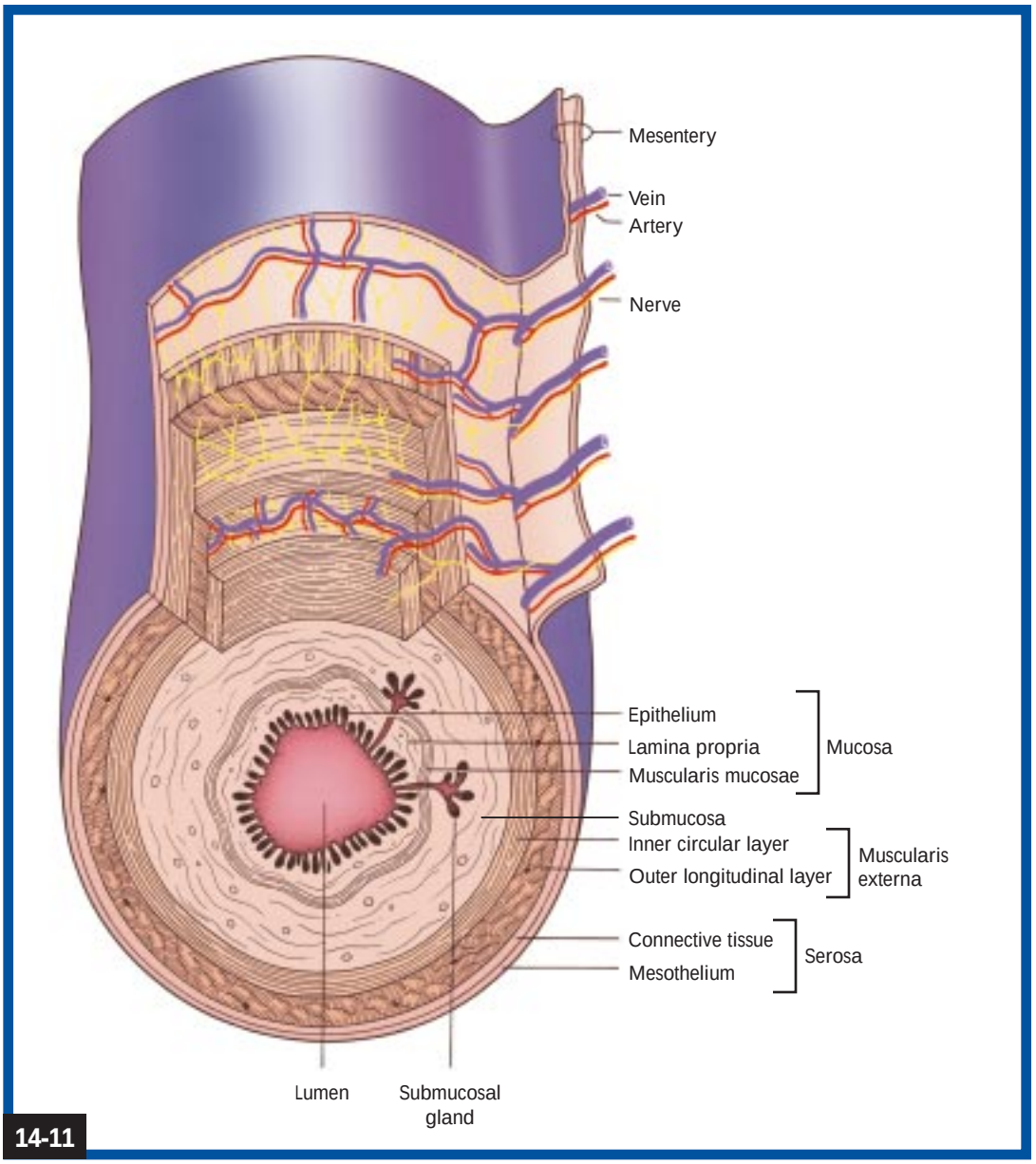

BASIC PLAN OF THE DIGESTIVE TUBE All parts of the digestive tube are built on this basic plan, with modifications in each organ appropriate to their different functions.

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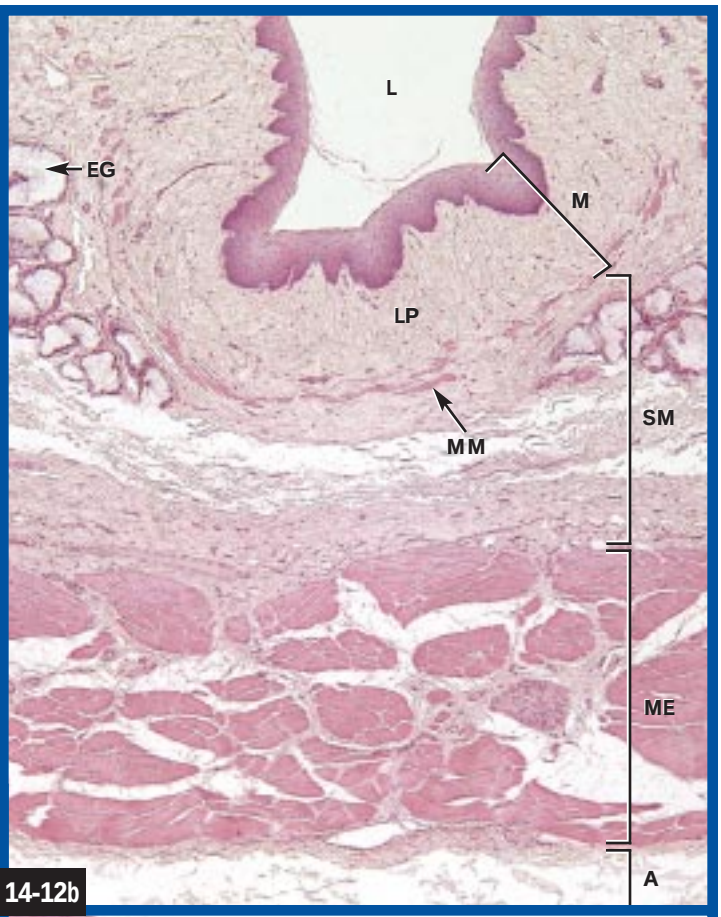

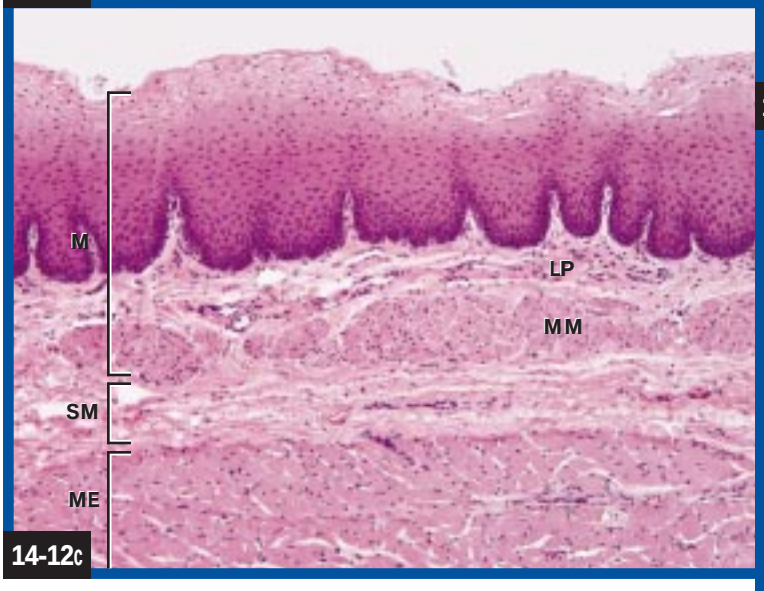

ESOPHAGUS (a) In this panoramic view, one can observe the collapsed lumen (L) of the esophagus when empty. *(X15)* (b) This specimen is from the upper third of the esophagus as evidenced by skeletal muscle in the muscularis externa. Also note the esophageal glands (EG) in the submucosa and the incomplete muscularis mucosae. *(X60)* (c) Note the thick nonkeratinized stratified squamous epithelium and the thick, but still incomplete muscularis mucosae. The skeletal muscle in the muscularis externa tells us that the specimen is from the upper third of the esophagus. *(X65)* (d) Esophageal glands (EG) secrete lubricating mucus for the inner lining of the esophagus. Note the duct of one gland passing to the surface. *(X55)* Key to symbols used: **M** = mucosa, **SM** = submucosa, **ME** = muscularis externa, **A** = adventitia, **LP** = lamina propria, **MM** = muscularis mucosae.

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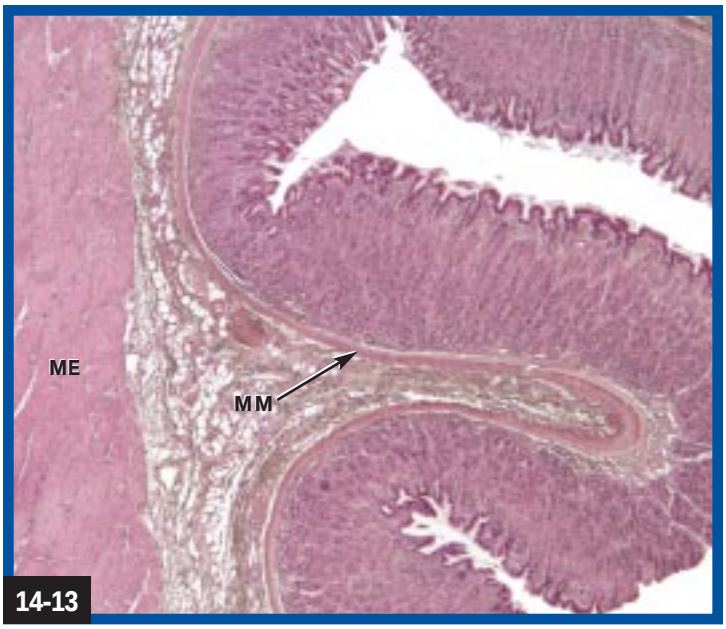
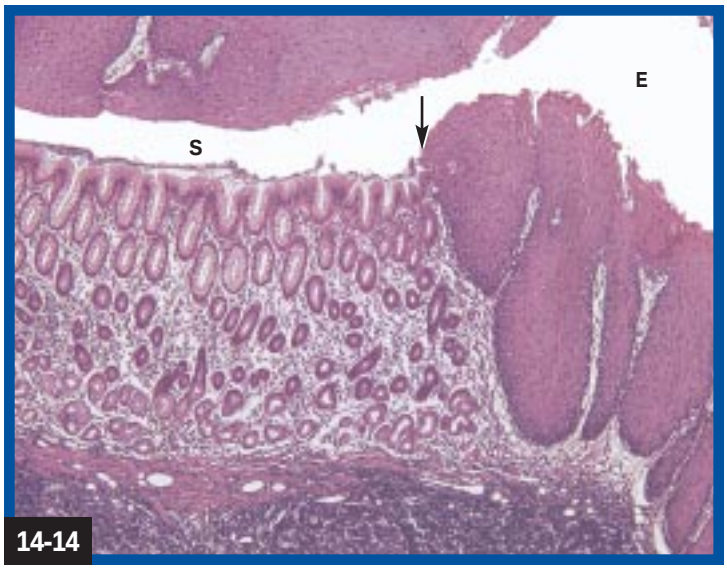
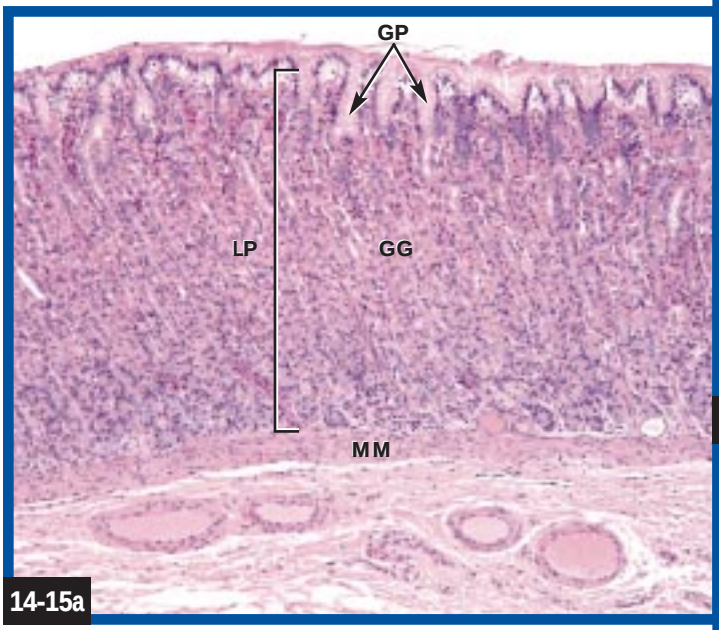
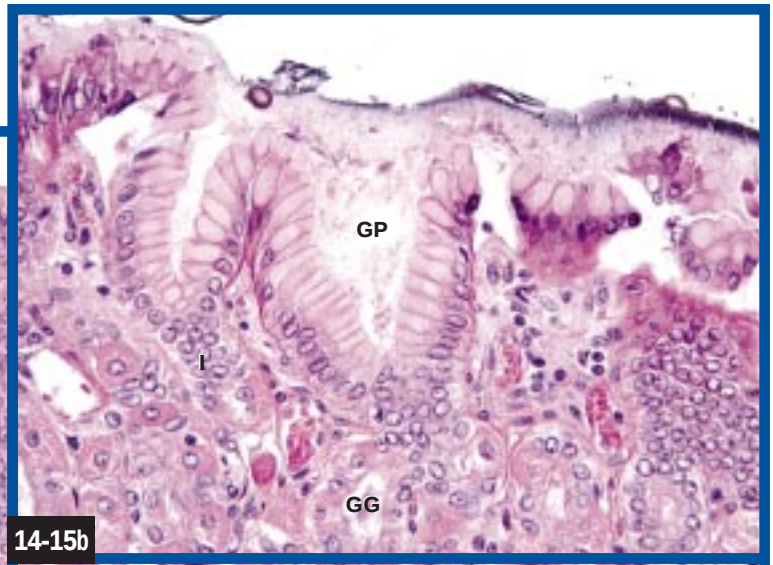


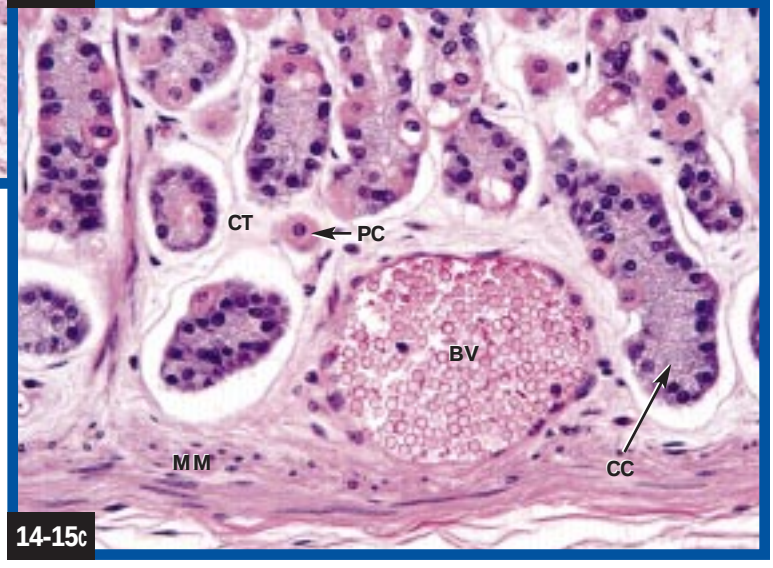
GASTRIC RUGAE The stomach's mucosa presents nonpermanent longitudinal folds called rugae. These flatten as the stomach fills with food. One ruga is shown in this micrograph. Notice that the muscularis mucosa (MM) is folded, indicating the whole mucosa is folded, but the muscularis externa (ME) is not. *(X20)*



ESOPHAGEAL-CARDIAC JUNCTION The stratified squamous epithelium stops abruptly (arrow) and becomes a simple columnar epithelium where the esophagus (E) joins the cardiac stomach (S). All other layers are continuous between the two organs. *(X50)*







GASTRIC MUCOSA The stomach's mucosa is lined with a simple columnar epithelium. Depressions called gastric pits (GP) lead to gastric glands (GG) which extend to the muscularis mucosae (MM) and occupy most of the lamina propria (LP). (a) This micrograph shows the entire thickness of the gastric mucosa (*X50*). (b) Shown here are gastric pits and the beginnings of gastric glands. Note the stomach's surface is lined with mucus cells, which are also found down in the pits, and the isthmus (I) and neck of the glands. (*X265*) (c) This micrograph shows that gastric glands extend down to the muscularis mucosae. Enzyme secreting chief cells (CC) and HCl secreting parietal cells (PC) are indicated. Note the blood vessel (BV) and how little connective tissue (CT) there is between glands. *(X265)*

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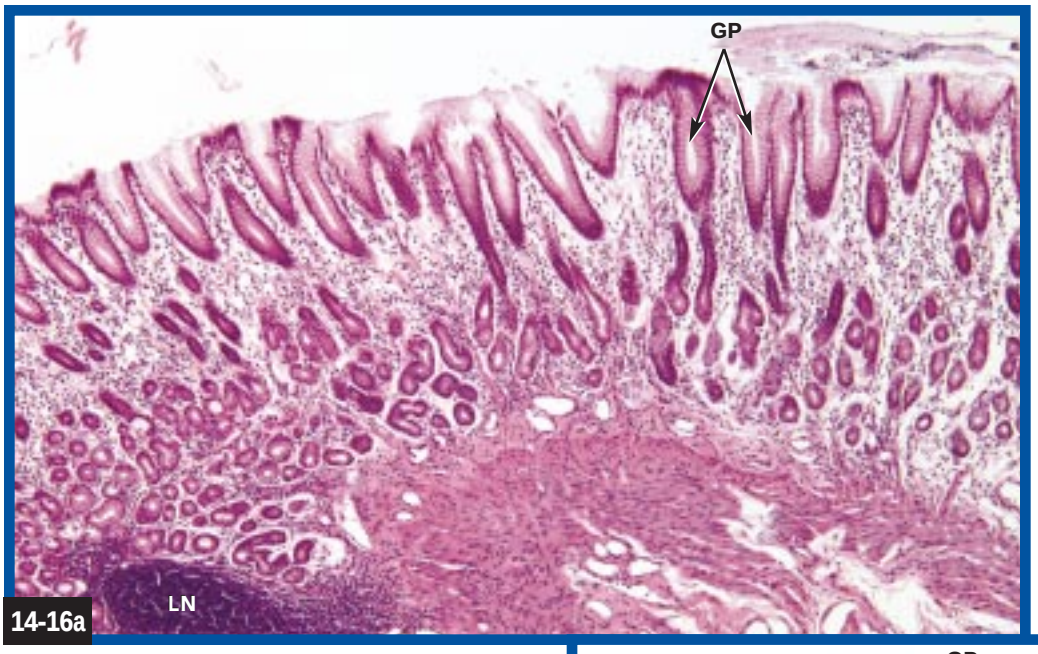
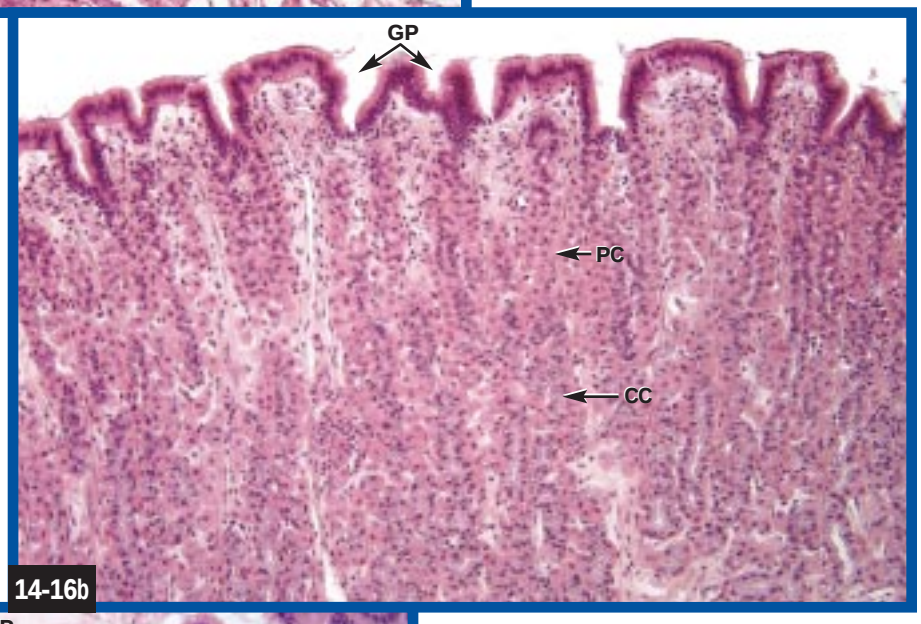
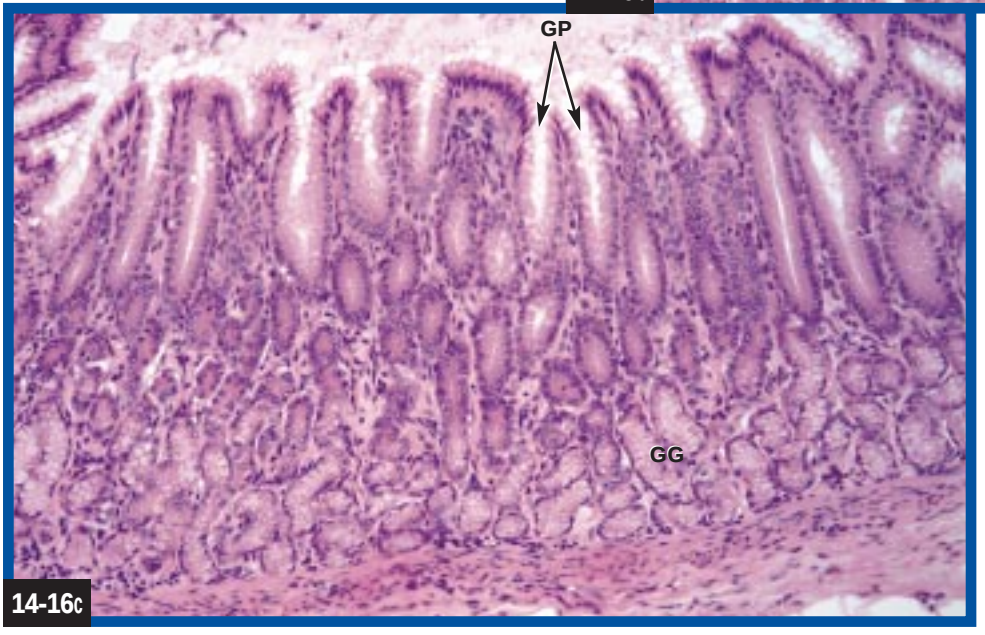


STOMACH REGIONS The mucosa of each part of the stomach has a characteristic appearance. (a) In the cardiac stomach the gastric pits (GP) are deep and the cardiac glands secrete mostly mucus. Note the lymphatic nodule (LN). (*X65*) (b) The body and fundus of the stomach have shallow pits and typical gastric glands with chief (CC) and parietal cells (PC). (*X115*) (c) Deep pits extending down about half the mucosa's thickness characterize the pyloric region. The gastric glands (GG) secrete mucus. (*X130*)





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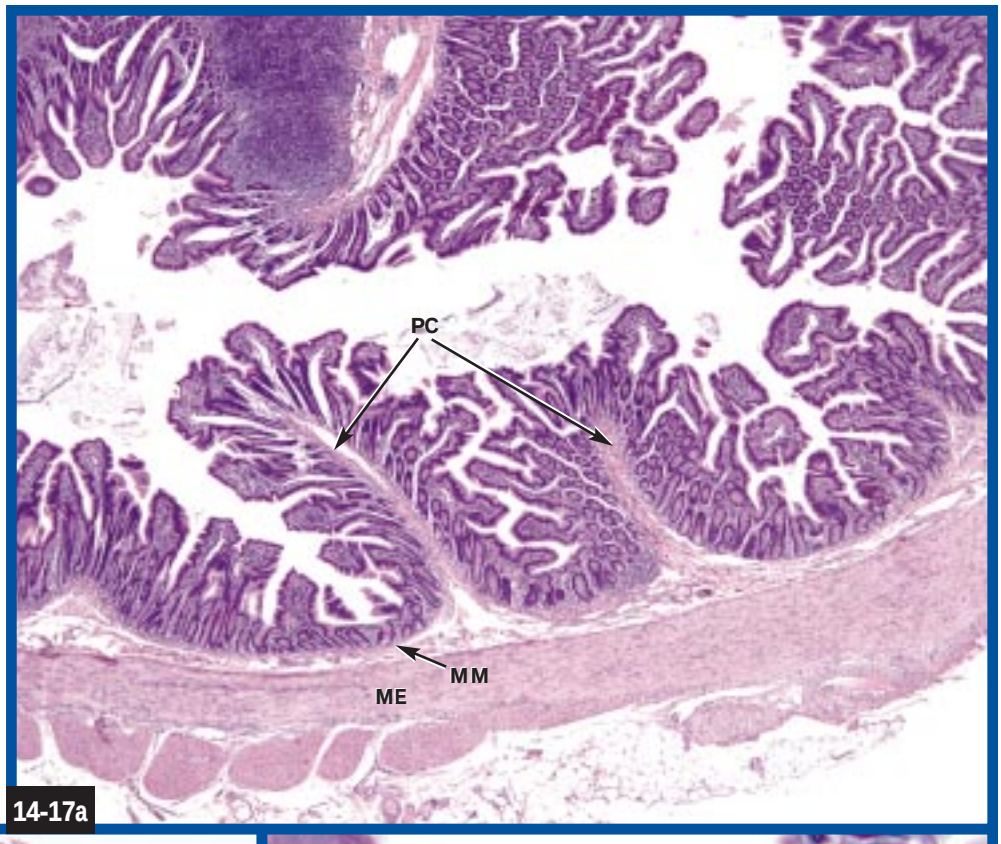
INCREASING SURFACE AREA IN THE SMALL INTESTINE The mucosa of the small intestine has several modifications to increase surface area for absorption. (a) Plicae circulares (PC) are permanent mucosal folds. As with rugae, note that the muscularis mucosae (MM) is folded, but the muscularis externa (ME) is not. (*X25*) (b) Villi (V) extend from the mucosal surface. In this micrograph, the villi are projecting from the surface of a plica. Note that the muscularis mucosae does not follow the contours of the villi. (*X25*) (c) Shown here are the adjacent sides of two villi. The simple columnar epithelium covering villi is modified with microvilli, which in light micrographs is seen as a brush border (BB). Also note the goblet cells (GC) and lymphocytes (L). *(X660)*



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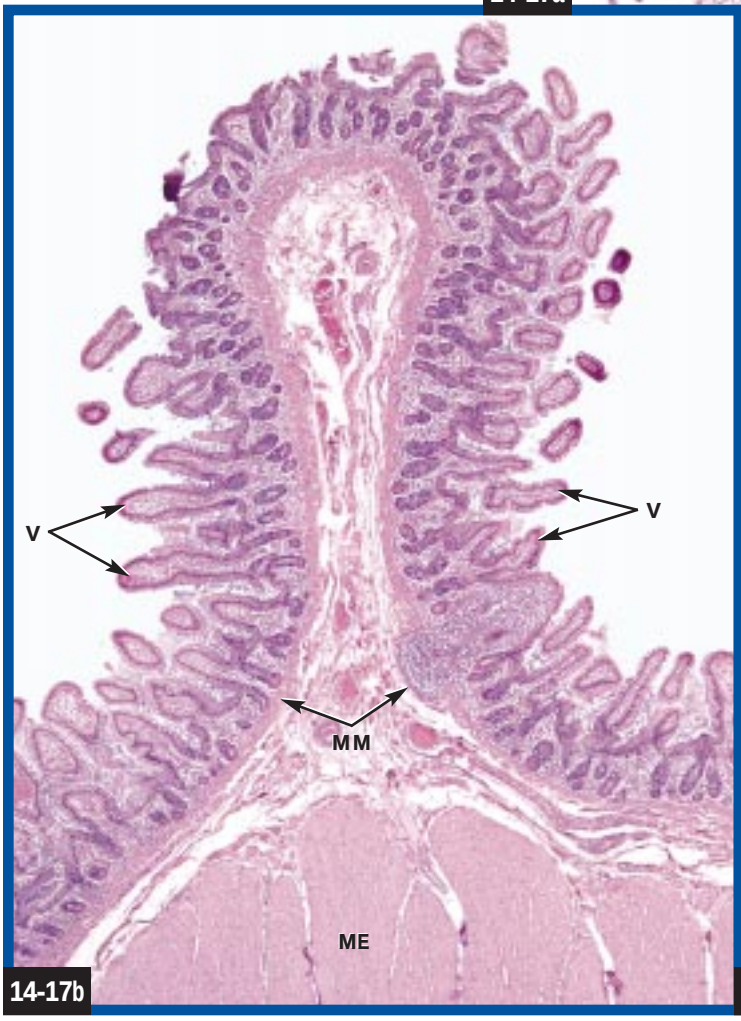

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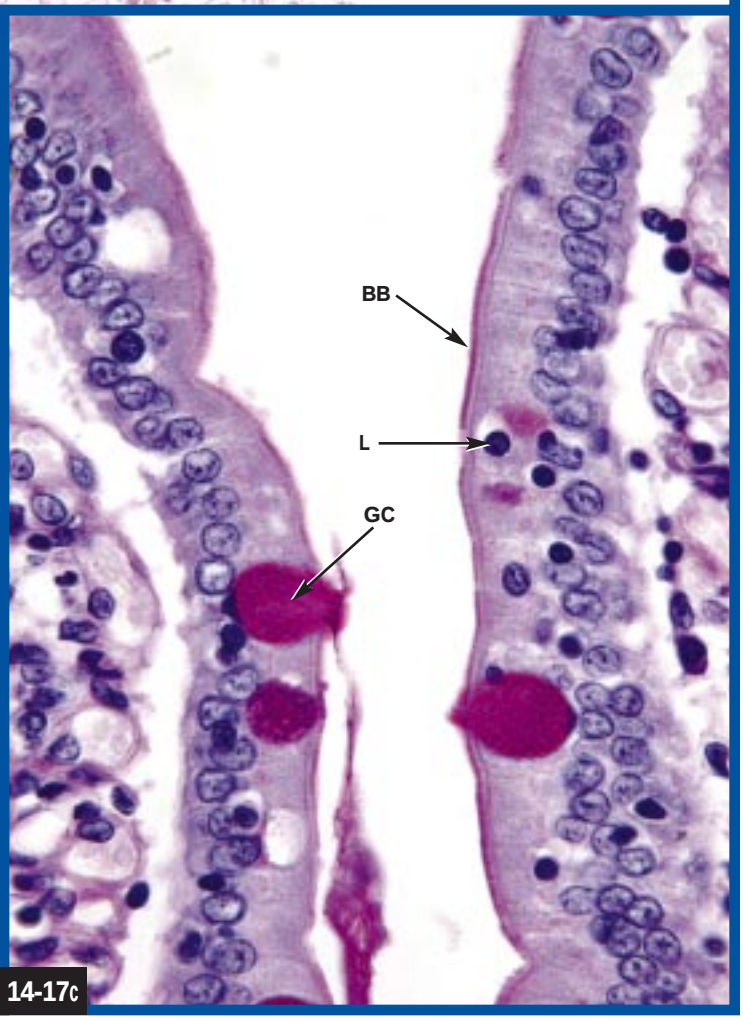

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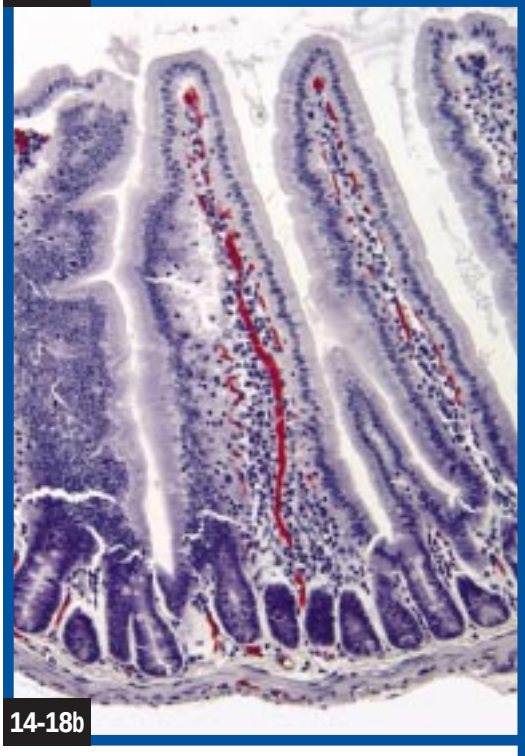

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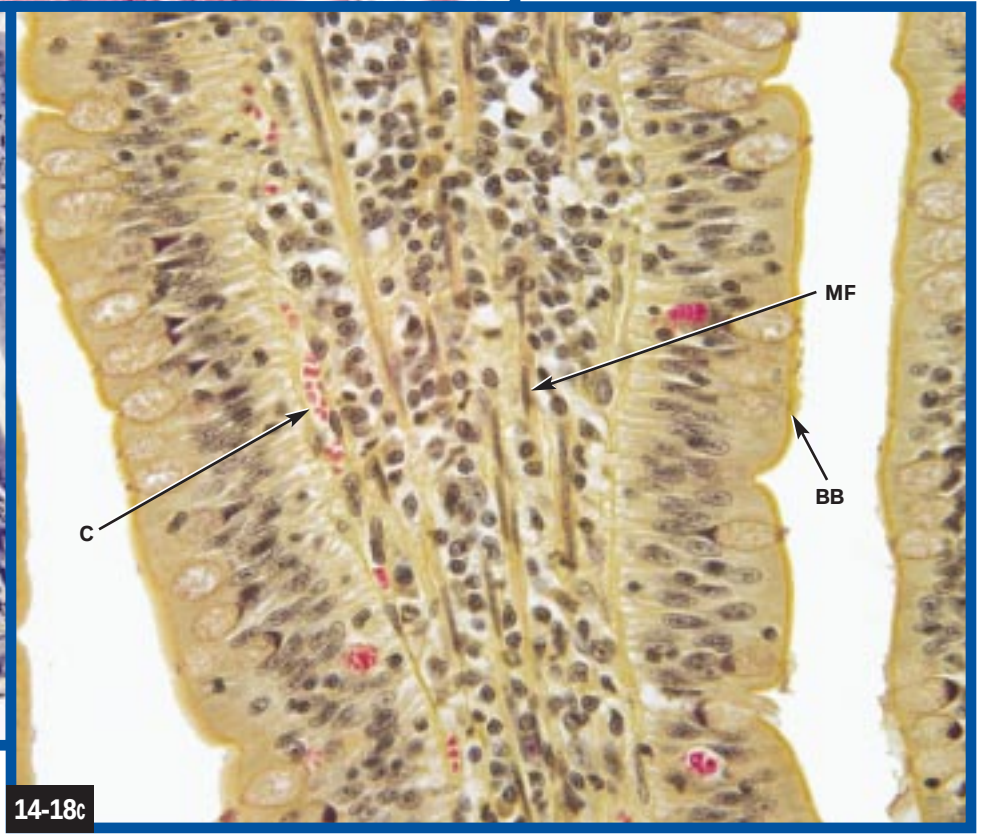

14-18c

INTESTINAL MUCOSA The intestinal mucosa has villi (V) projecting from it and crypts of Lieberkühn (CL) projecting into it. The intervillous spaces (IV) are much larger than the space within the crypts, providing a clue as to where the intestinal surface actually is. Simple columnar cells (SC), goblet cells (GC), and Paneth cells (P) are present in the epithelium. (a) The level of the intestinal surface is indicated with a line at the right of the field. Villi project up from the surface and crypts project below the surface. Note the dark nuclei of lymphocytes in the lamina propria (LP), the muscularis mucosae (MM) and the submucosa (SM). (*X130*) (b) This specimen has had its blood vessels injected with a red dye. Note the capillaries in the lamina propria of the villi. (*X130*) (c) This micrograph shows smooth muscle fibers (MF) and a capillary (C) in the lamina propria. A clear brush border (BB) is also visible. *(X400)*

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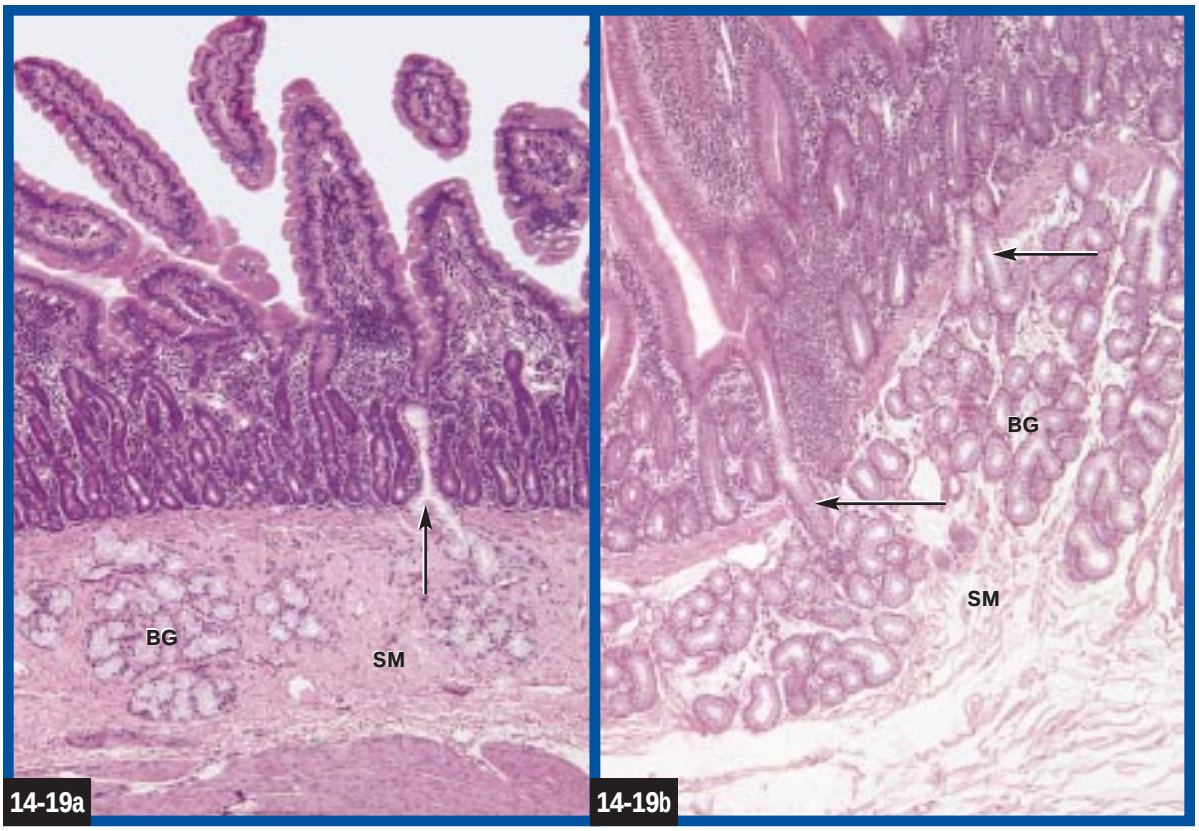
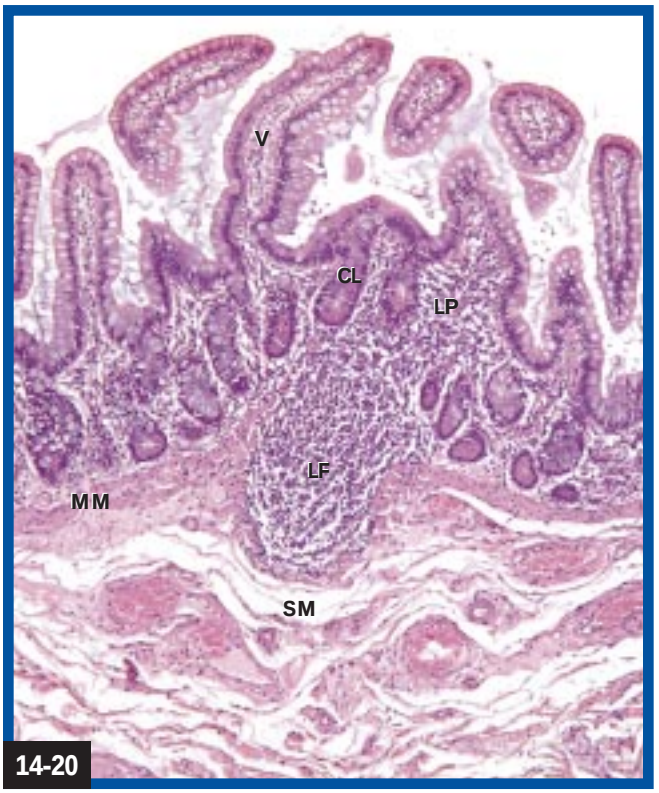


DUODENUM The duodenum is identifiable by mucus secreting Brünner's glands (BG) in the submucosa (SM). (a) In this micrograph, the Brünner's glands are not very dense. One gland is seen emptying into a crypt (arrow). *(X65)* (b) The Brünner's glands are much denser in this specimen. Several glands are seen emptying into the crypts (arrows). *(X65)*



JEJUNUM The jejunum has no diagnostic feature of its own, so tentative identification may be made based on the absence of Brünner's glands and Peyer's patches. Note the lymphatic follicle (LF) in the submucosa (SM) and lamina propria (LP). Villi (V), crypts (CL), and the muscularis mucosae (MM) are also visible. *(X65)*

ILEUM The ileum has distinctive aggregations of lymphatic follicles called Peyer's patches (PP) in the submucosa and sometimes extending into the lamina propria. Note the plica circulares (PC). *(X25)*

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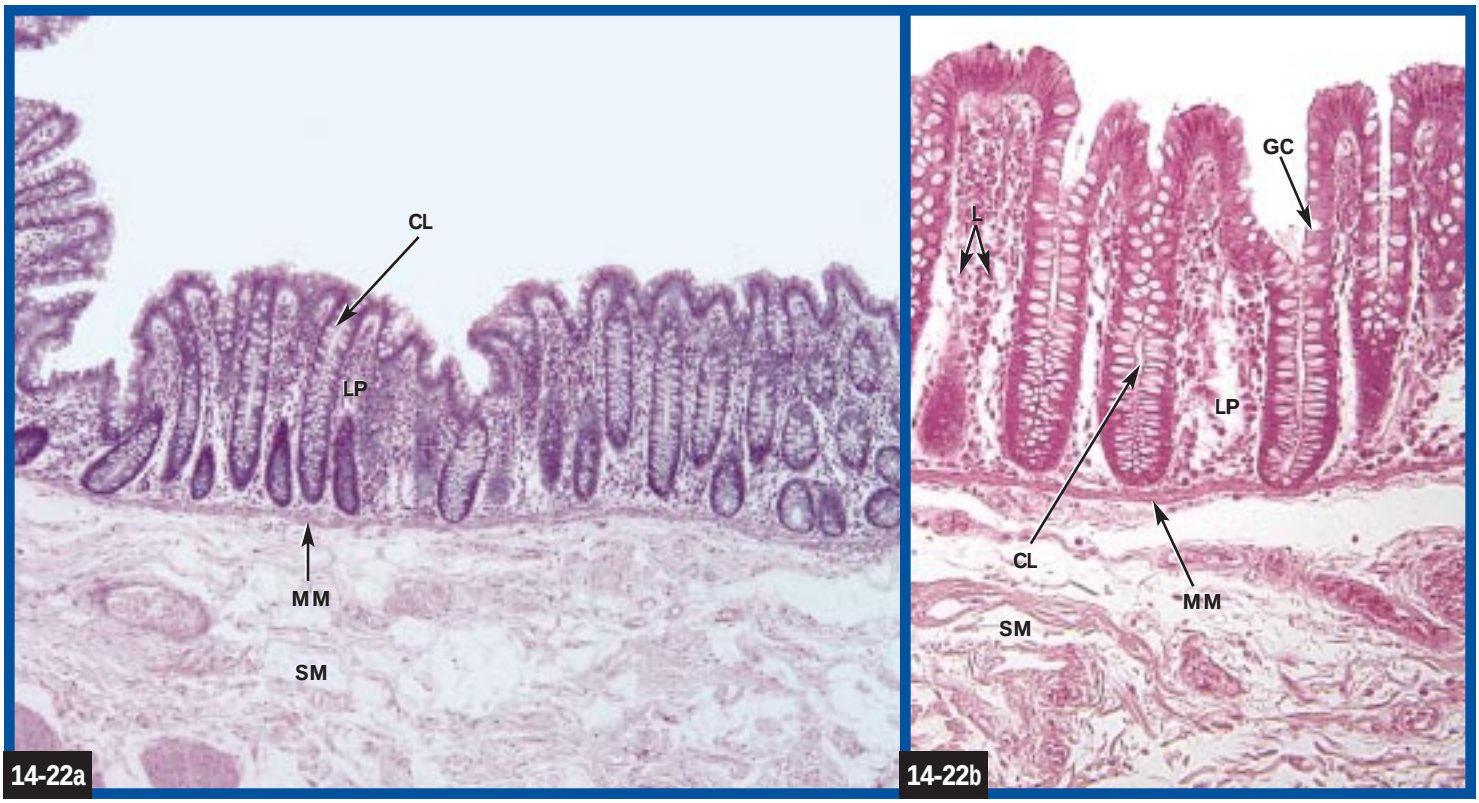
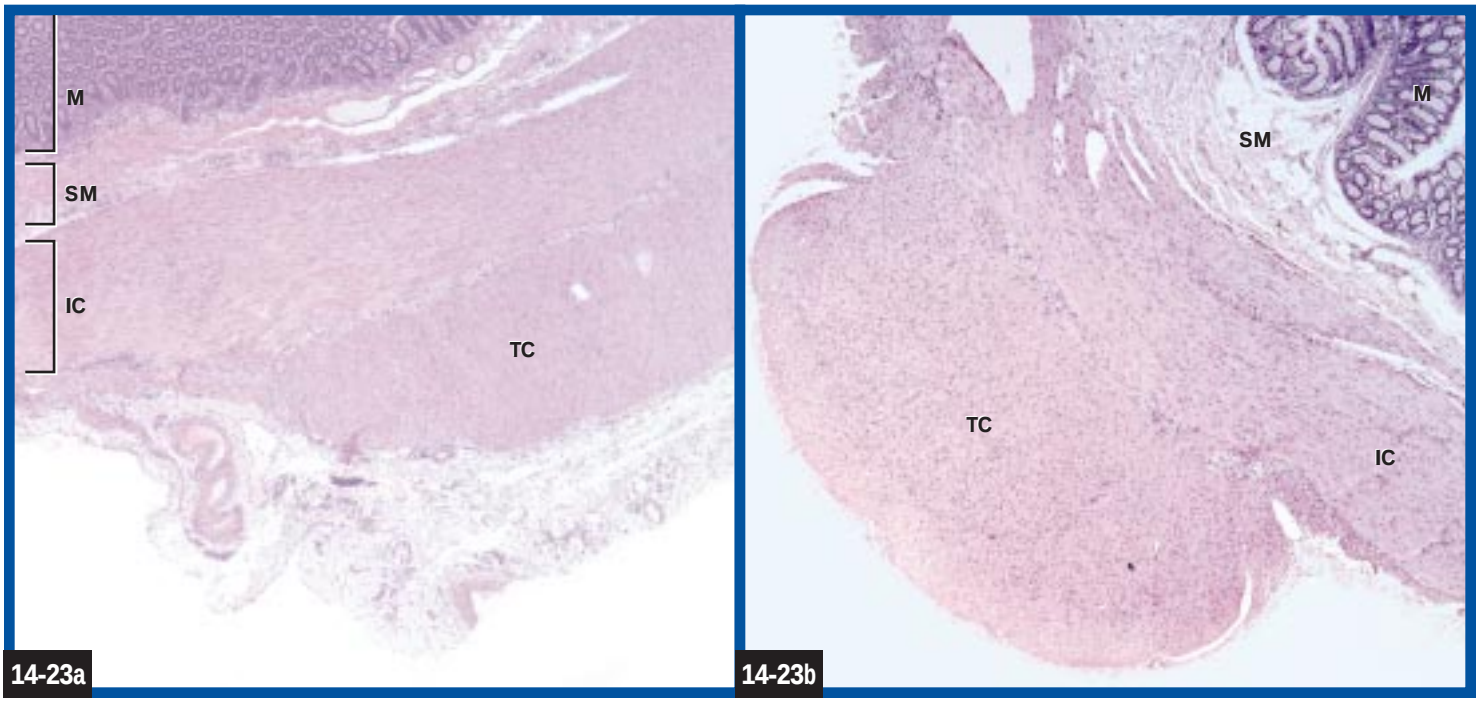


COLON MUCOSA The colon's mucosa is characterized by long, straight crypts of Lieberkühn (CL) that penetrate the lamina propria (LP) to the muscularis mucosae (MM). The submucosa (SM) is also visible. Note the abundant goblet cells (GC) in the epithelium and the lymphocytes (L) in the lamina propria. Micrograph (a) is X65; micrograph (b) is X130.



TAENIA COLI MUSCLES The longitudinal layer of muscle in the colon is thicker in three strips called taenia coli muscles (TC). As evidenced by these micrographs, the taenia coli are not exceptionally thick for a longitudinal muscle layer. It is the thin regions between them that make them prominent. Also visible are the mucosa (M), submucosa (SM), and inner circular (IC) layer of muscle. Both micrographs are X25.

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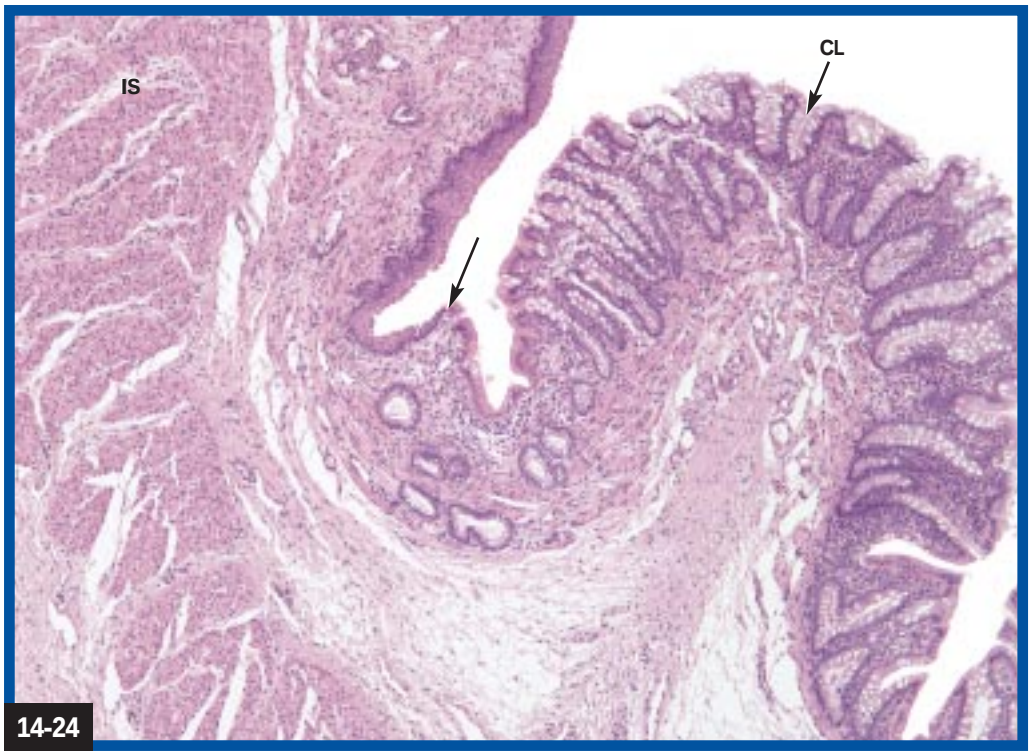
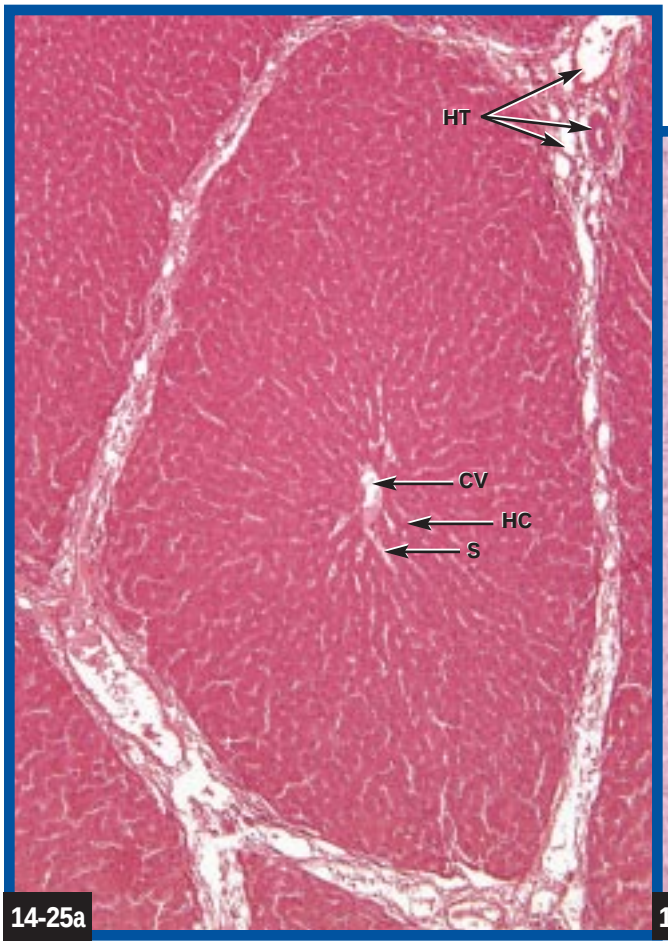
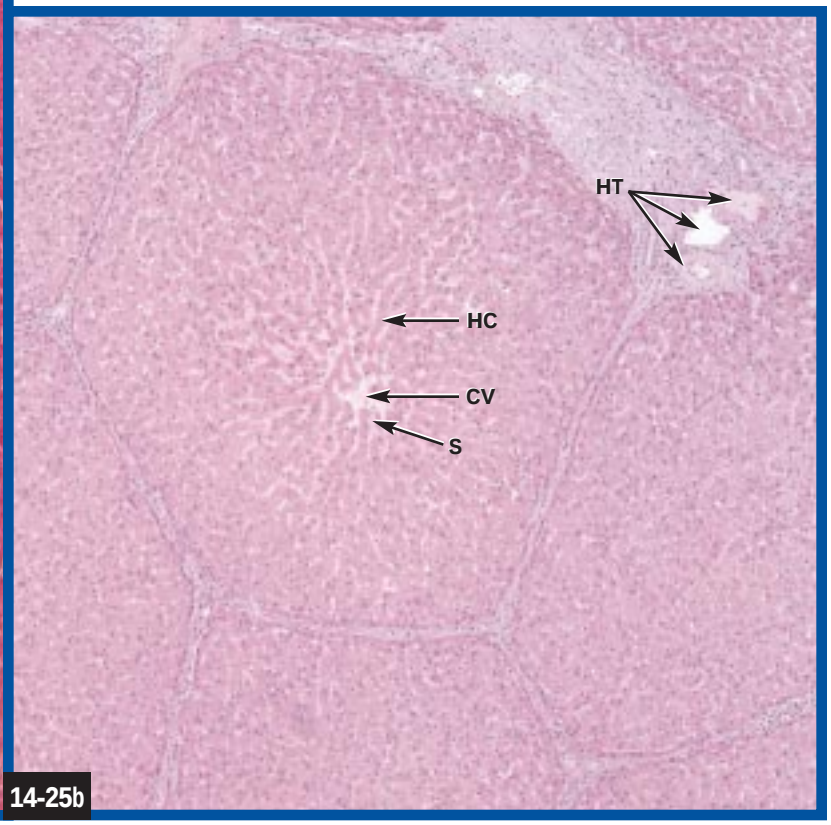
RECTOANAL JUNCTION Compared to the colon, the rectum has shorter crypts (CL) with more goblet cells. At the rectoanal junction (arrow), the simple columnar epithelium abruptly changes to a nonkeratinized stratified squamous epithelium. The internal anal sphincter (IS) is a thickening of the inner circular muscle layer. (*X65*)







LIVER LOBULES The liver is divided into lobules, which are not very distinct in humans. These specimens are from other mammals to illustrate lobule structure. At the center of the lobule is the central vein (CV). Radiating outward like spokes on a wheel are cords (HC) of hepatocytes, between which are blood sinusoids (S). Hepatic triads (HT) composed of branches of the hepatic artery, hepatic portal vein, and bile duct are present at corners of the lobules. (a) X60, (b) X65.

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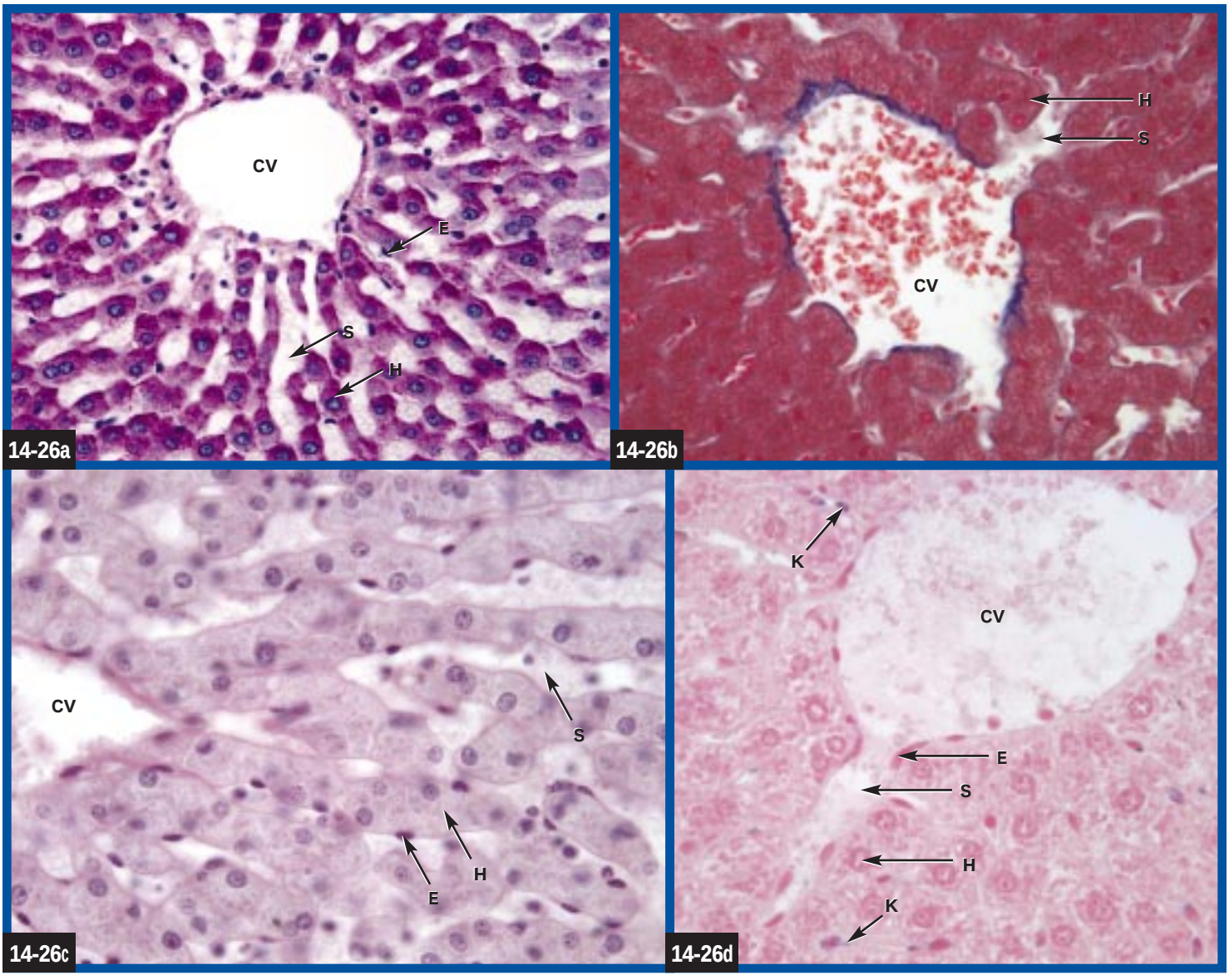
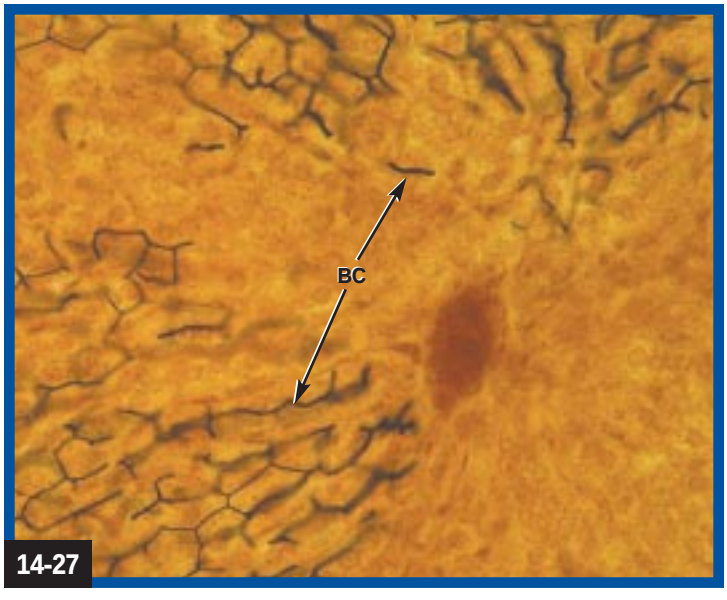


CELLS OF THE LOBULE Hepatocytes (H) are arranged into cords that are separated by the sinusoids (S), which are lined with endothelial cells (E). Sinusoids drain into the central vein (CV). Phagocytic Kupffer cells (K) are also found in the sinusoids. (a and b) Note the continuity of the sinusoids and central vein and the reddish purple staining glycogen in the hepatocytes in (a). Both micrographs are X265. (c) Note the dark staining nuclei of the endothelial cells, which form an incomplete barrier between the sinusoids and the hepatocytes. (*X400*) (d) Kupffer cells in this preparation have phagocytosed black particles and are easily distinguished from the endothelial cells. *(X400)*.



BILE CANALICULI Bile production is among the many functions performed by hepatocytes. Bile canaliculi (BC) are tiny channels formed between hepatocytes that lead to a branch of the bile duct in the hepatic triad. These bile canaliculi have been injected with a black dye to make them more visible. Notice that they are only found over hepatocytes, not in the sinusoids. Normally, blood and bile don't mix. *(X265)*

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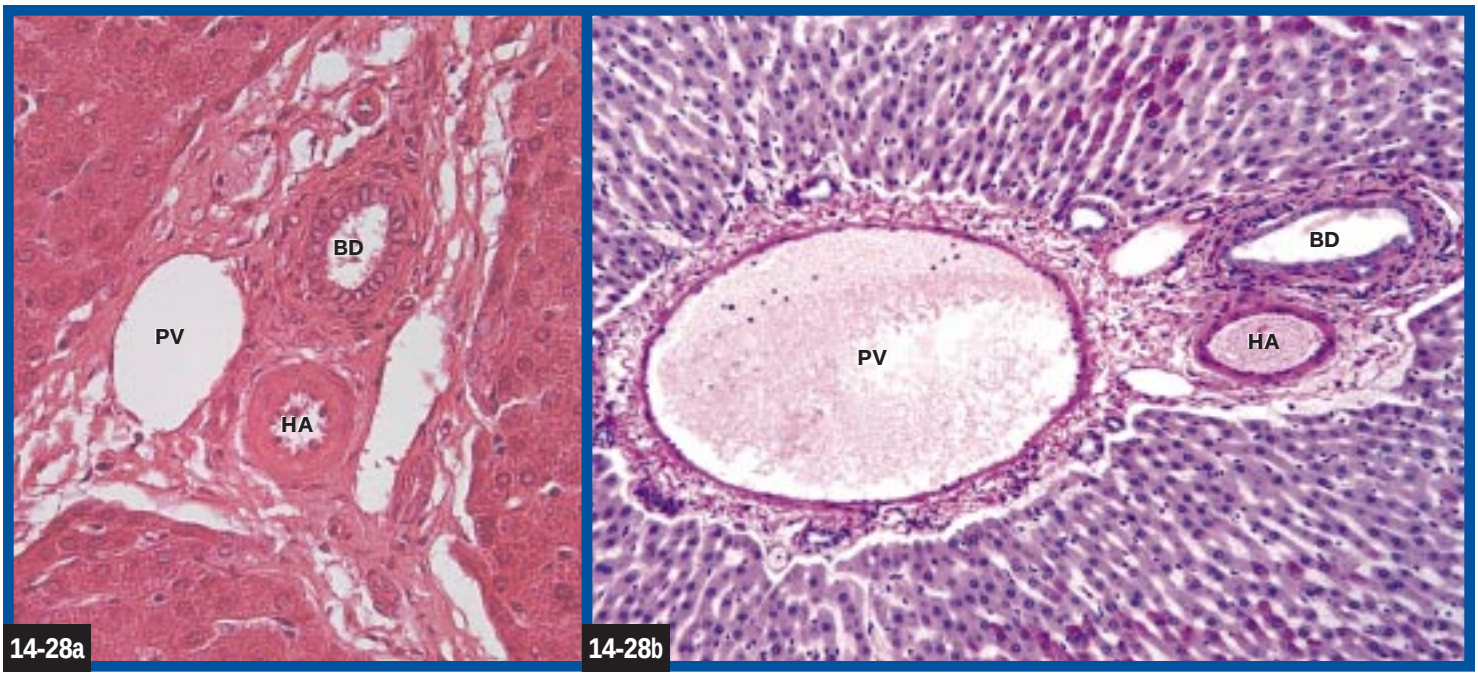
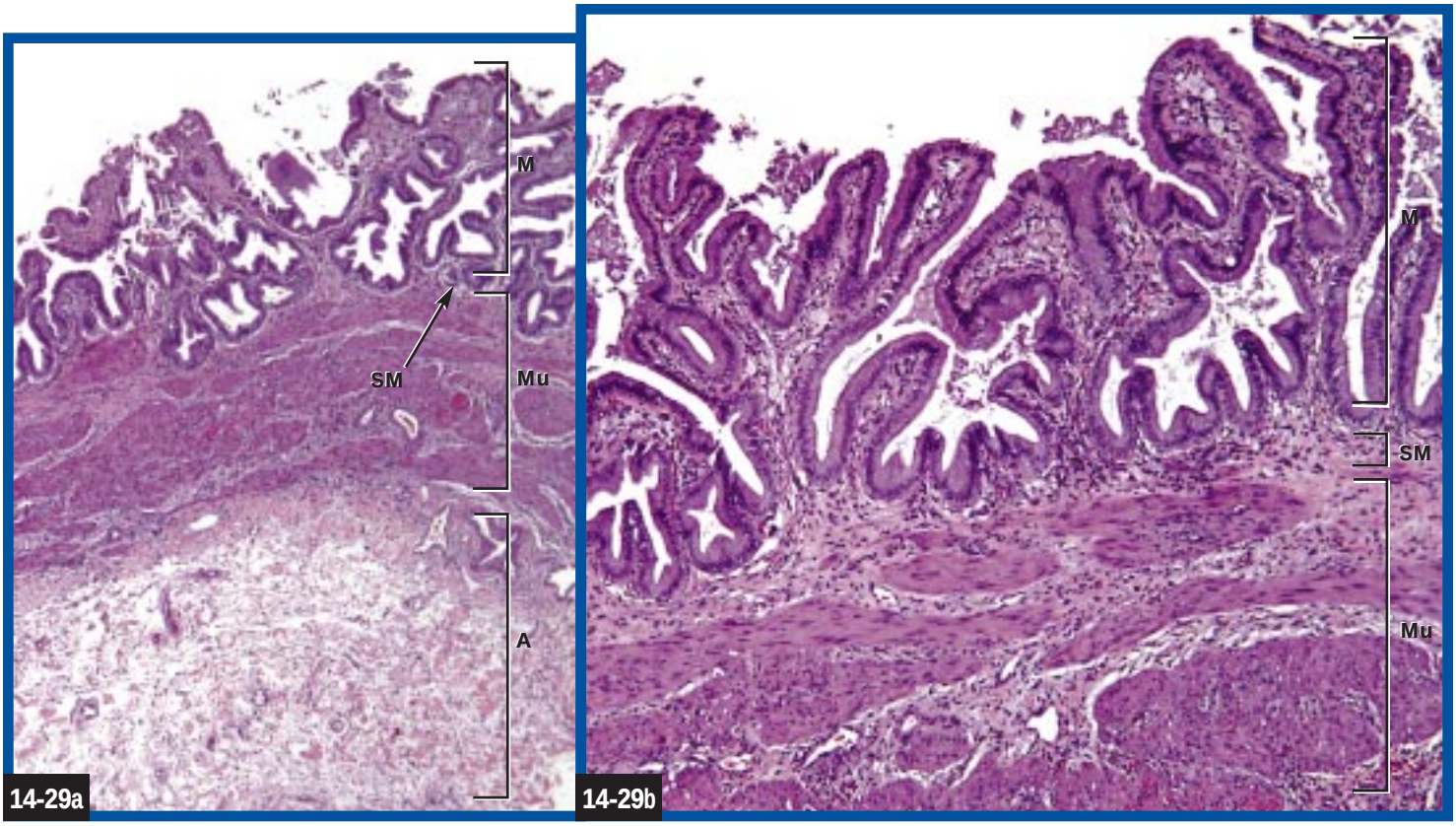


HEPATIC (PORTAL) TRIAD Branches of the hepatic artery (HA), hepatic portal vein (PV), and bile duct (BD) travel together throughout the liver and form a hepatic triad. (a) Notice that the triad components are not unusual in appearance. That is, the artery is smaller and has a thicker wall than the vein, and the bile duct is lined with a simple cuboidal epithelium. (*X265*) (b) This specimen was sectioned just above a branch point, so each component is represented more than once. *(X265)*



GALL BLADDER The mucosa (M) of the gall bladder is lined with a simple columnar epithelium and is folded longitudinally. The submucosa (SM) is a loose connective tissue. Deep to it is the muscularis (Mu), which is made of smooth muscle arranged into indistinct longitudinal, circular and oblique layers. A thick adventitia (A) covers the outer surface. Micrograph (a) and (b) were magnified X25 and X65, respectively.

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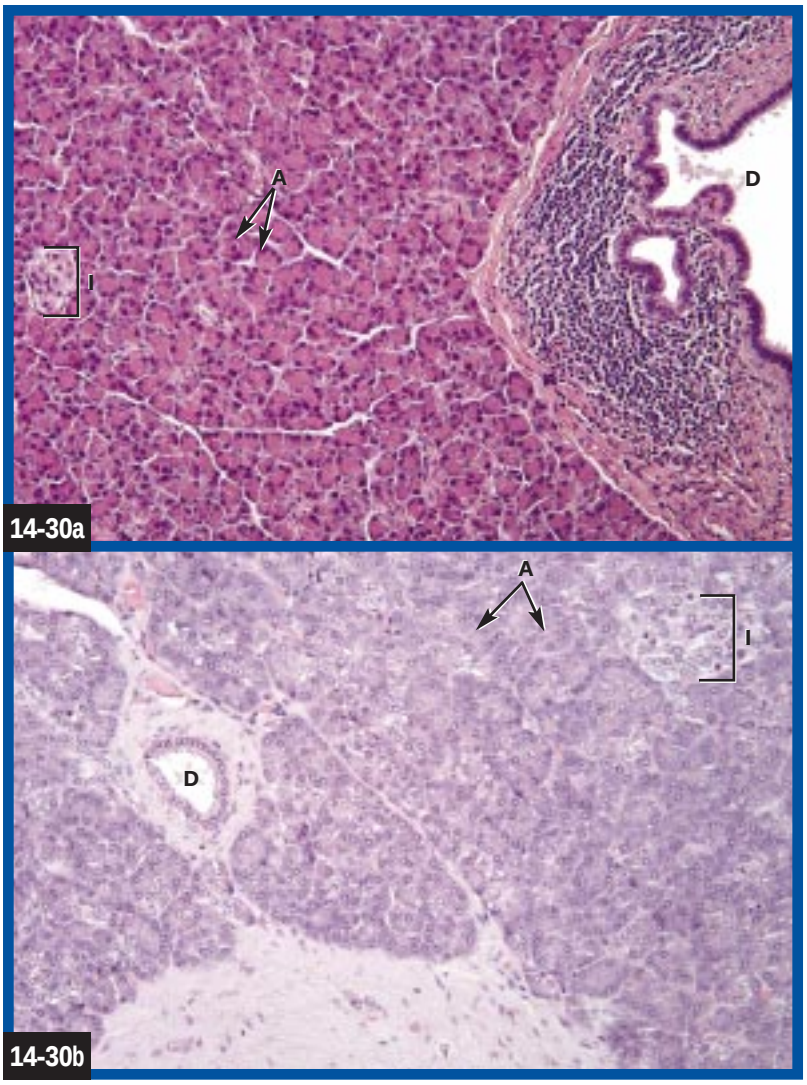
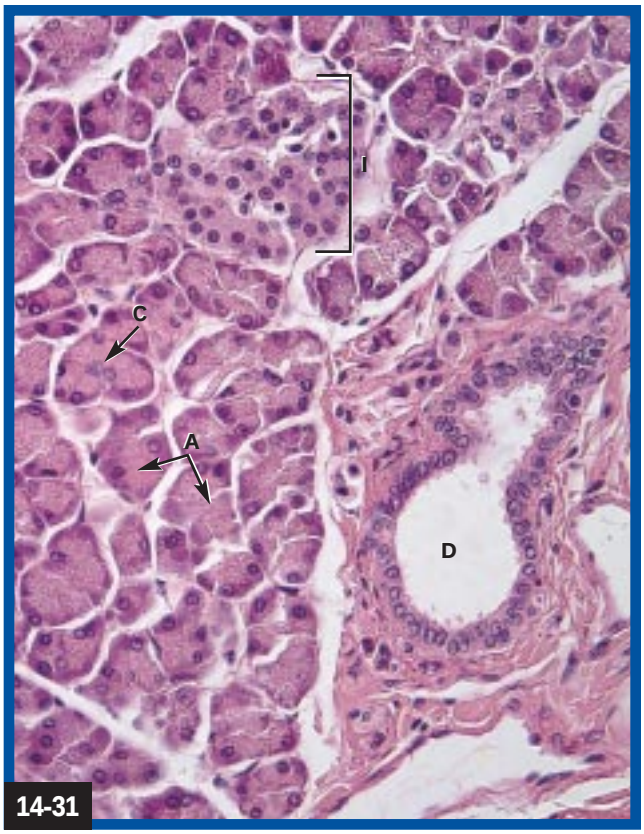


PANCREAS The pancreas has an endocrine component and an exocrine component. The endocrine islets of Langerhans (I) secrete the hormones insulin and glucagon. The exocrine pancreatic acini (A) secrete pancreatic juice, an alkaline fluid rich in digestive enzymes. Interlobar ducts (D) are also present and are recognizable by the connective tissue covering. (a) Note the lymphatic tissue in the interlobar duct at the right. (*X115*) (b) The light-staining region at the bottom is a portion of a large interlobar duct. (*X115*) Also see Figure 10-9.



PANCREAS DETAIL This micrograph illustrates pancreatic acini (A), an islet of Langerhans (I), and a small interlobar duct (D). Note the eosinophilic secretory granules at the apices of the exocrine cells. Two centroacinar cells (C), which are lining cells of the intercalated duct, are also visible. *(X265)*

AMPULLA OF VATER The common bile duct and the main pancreatic duct join within the duodenal wall to form the ampulla of Vater (V), which delivers pancreatic juice and bile to the duodenum. Also visible in this micrograph are the pancreas (P) —note the lobes—and Brünner's glands (B). (*X25*)

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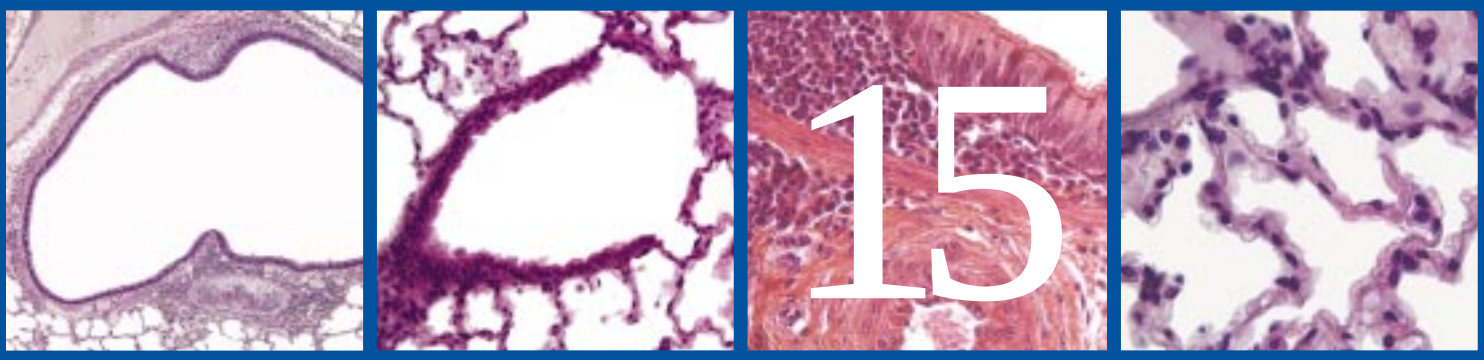
Respiratory System

CHAPTER 15



Introduction to the Respiratory System

The respiratory system is responsible for gas exchange between the environment and lung capillaries. Anatomically, it is divided into the **upper respiratory tract** including the nasal cavity, pharynx, and larynx, and a **lower respiratory tract** composed of the trachea, bronchial tree, and lungs. Besides conducting air, other important functions of the upper respiratory tract include warming and moistening the air to prepare it for gas exchange, filtering it to prevent infection and the blockage of smaller airways, olfaction, and vocalization.

Functionally, the respiratory system is divided into a **conducting portion**, responsible for transmitting air to the lungs, and a **respiratory portion**, in which respiratory gas exchange occurs. The actual sites of gas exchange are called **alveoli**, microscopic sacs lined with simple squamous epithelium and surrounded by capillaries.

The abundant alveoli occupy the majority of lung volume, so a discussion of lung histology is primarily a discussion of alveolar anatomy. However, on a gross level, each lung is divided into lobes (three in the right lung, two in the left), which in turn are divided into segments (ten in the right lung, 8 in the left). The lung's surface is covered with serous membrane called **visceral pleura** (Figure 15-1).

Nasal Cavity

The **nasal cavity** is formed from a framework of bone and cartilage with a vascular mucous membrane covering. It is divided by the nasal septum into right and left cavities. Just inside the **external naris** of each side is the **vestibule**, which is lined with stratified squamous epithelium and thick hairs, called **vibrissae**. These act as a coarse filter.

Most of the nasal cavity is lined by **respiratory epithelium**, a **pseudostratified ciliated columnar epithelium (PSCC)** with **goblet cells** (Figures 9-1 and 15-2). Deep to the epithelium is a very vascular **lamina propria** that also contains serous and mucous glands. Secreted mucus maintains a moist environment that humidifies the air. It also traps inert particles and microorganisms in inspired air, and the cilia sweep the mucus to the throat where it is swallowed. The blood vessels of the lamina propria are responsible for providing the heat to warm air.

In the upper nasal cavity and superior nasal conchae, respiratory epithelium is replaced with **olfactory epithelium** (Figures 9-1 and 15-2). It differs from typical respiratory epithelium in its thickness and lack of mucous cells. Bipolar neurons act as **olfactory receptor cells**. They are chemoreceptors. Short **basal cells** and taller **sustentacular cells** are also present, although they are difficult to differentiate in standard H&E preparations. **Bowman's glands** in the lamina propria produce a watery secretion that dissolves chemicals and makes them more able to stimulate the receptors.

Larynx

The **larynx** is positioned between the pharynx and the trachea. It is made of a cartilagenous (mostly hyaline) framework lined with mucous membrane consisting of PSCC and a lamina propria. On its anterior and superior aspect is the **epiglottis** (Figure 15-3), which is made of a leaf-shaped elastic cartilage covered with stratified squamous epithelium

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on its superior part. It closes the opening to the larynx to prevent food from "going down the wrong pipe" when swallowing.

Within the larynx are two pairs of mucosal folds. The **true vocal folds** (Figure 15-4) are involved in phonation and are the superior pair. The **false vocal folds** are inferior. The **vocal ligaments** are deep to the stratified squamous epithelium of the true folds. Muscular action increases and decreases tension on the vocal folds to alter the pitch of the sound produced.

Trachea

The **trachea** (Figure 15-5) is a tubular organ anterior to the esophagus. It begins at the junction with the larynx and continues to its bifurcation into the two **primary bronchi**. C-shaped hyaline cartilage rings provide support, while fibrous connective tissue filling between them provides flexibility.

Histologically, the trachea is composed of a **mucosa**, **submucosa**, and **adventitia**, and its structure establishes the basic plan for the rest of the respiratory tree (Figure 15-6). The mucosa is composed of a typical respiratory epithelium—a tall PSCC with goblet cells—and a fibrous lamina propria, often containing lymph follicles. An **elastic lamina** separates the lamina propria from the submucosa, which is made of dense irregular connective tissue. Various serous and mucous glands may be found in the submucosa. The adventitia is a fibroelastic connective tissue that houses the cartilagenous rings. The **trachealis muscle** (Figure 15-7), a band of smooth muscle, occupies the open posterior of the C-shaped rings.

Bronchial Tree

The trachea branches into two **primary bronchi**, each of which goes to a lung. Once in the lung, primary bronchi divide to form **secondary (lobar) bronchi**. (From the secondary bronchi on, all branches are intrapulmonary.) There are three secondary bronchi supplying the three lobes of the right lung and two supplying the two lobes of the left lung. Secondary bronchi divide to form **tertiary (segmental) bronchi**, each of which supplies a distinct lung segment. Further branching produces, in order, **bronchioles**, **terminal bronchioles**, **respiratory bronchioles**, **alveolar ducts**, and **alveolar sacs**.

The general trends seen in the bronchial tree are as follows:

- The diameter of the tubes decreases.
- The epithelium as a whole gets shorter and the cells get flatter, going from a tall PSCC in the trachea to a simple squamous in the alveoli.
- There is a decrease in the size of the cartilage, going from C-shaped rings in the trachea, to more plate-like in the bronchi, to absent in the bronchioles.
- There is an increase (relative to the size of the tube) in the amount of smooth muscle and elastic tissue.
- The number of glands and goblet cells decreases.

The bronchi (Figure 15-8) resemble the trachea, but the cartilage is plate-like, with the plates being found on all sides (that is, there is no open side as with the C-shaped rings). There are smooth muscle and elastic fibers present, as are glands and lymph follicles, which are especially seen at branch points of the airways. The epithelium is PSCC with goblet cells that gets progressively shorter.

Bronchioles (Figures 15-9 and 15-10) are about 1 mm in diameter or less, but they are easily identified due to their absence of cartilage in the wall. The epithelium is generally a simple ciliated columnar in larger bronchioles that transitions into a simple ciliated cuboidal, and then to a simple nonciliated cuboidal in the smallest bronchioles. Goblet cells are only seen in the largest of bronchioles. **Clara cells** are also seen in bronchiolar epithelium and are identified by their dome-shaped apical surface. They provide a source of new cells and produce surfactant that reduces surface tension in the lungs (see page 179). Glands are absent from the lamina propria, but lymphoid tissue is often seen. Spiral layers of smooth muscle occupy a majority of the wall.

The conducting portion of the bronchial tree ends with the **terminal bronchioles**. These are less than 0.5 mm in diameter. The epithelium is a simple cuboidal, some ciliated, with Clara cells. Only a couple of muscle layers are present.

Terminal bronchioles divide to produce **respiratory bronchioles**, which represent the beginning of the respiratory portion of the bronchial tree (Figures 15-9 and 15-11). These histologically resemble terminal bronchioles but are identifiable by the presence of alveoli in their walls. It is in the distal portion of respiratory bronchioles that cuboidal cells no longer have cilia.

As one progresses through the respiratory bronchioles, the alveoli become more and more numerous. Eventually, the wall is exclusively alveoli and the bronchiole has become an **alveolar duct** (Figures 15-9 and 15-12). A smooth muscle cell is positioned around the opening of each alveolus giving the appearance of knobs at the entrance of the alveolus to the alveolar duct. At the end of the alveolar duct are a few clusters of alveoli called **alveolar sacs**, which have a common opening called the **atrium**.

Alveoli

The diameter of an alveolus is about 200 µm, and between the two lungs there are about 300 million of them with a total surface area of approximately 140 m^2. The extensive surface area and the thin alveolar wall make them efficient in gas exchange with the blood. It also accounts for the spongy consistency of the lungs on a gross level.

There are three cell types found associated with alveoli (Figure 15-13). These are the type I pneumocytes, type II

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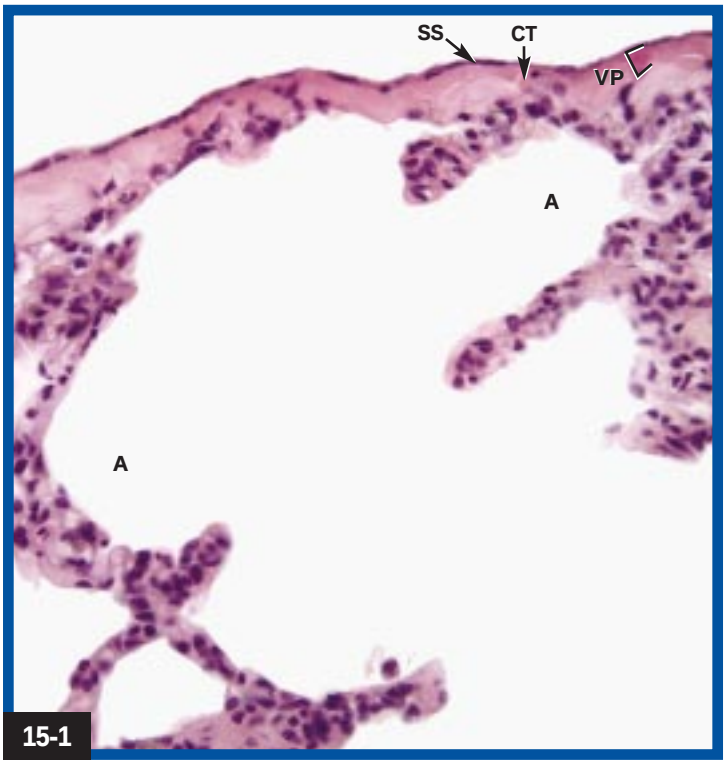
pneumocytes, and alveolar macrophages (dust cells). The majority of alveolar surface is covered by the simple squamous **type I pneumocytes**, although they comprise only about 5% of the alveolar cells. They are thin, even by squamous standards, having a thickness of as little as 80 nm. Their nuclei are infrequently seen due to the cells' extensive cytoplasm.

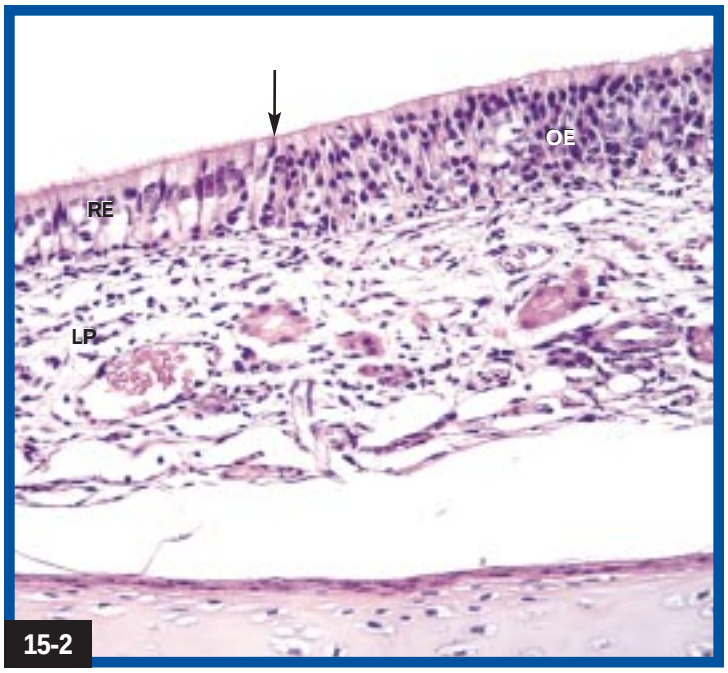
Type II pneumocytes (great alveolar cells) are cuboidal with a rounded apical surface and a central nucleus. They secrete surfactant that reduces surface tension and prevents the alveoli from collapsing during expiration.

Alveolar macrophages are often seen in the alveolar wall or lumen. They are derived from blood monocytes and phagocytose small particles that have slipped past the other defenses.

The **interalveolar septum** is composed of the epithelium of two alveoli separated by numerous capillaries supported by elastic and collagen fibers. Tiny openings called **alveolar pores** join adjacent alveoli through the septum and allow pressure equalization within the various lung compartments. The actual **blood-air barrier** is composed of the type I pneumocytes and capillary endothelium, plus their fused basal laminae. It is through these layers oxygen and carbon dioxide must diffuse during gas exchange between the air and blood.



VISCERAL PLEURA The outer surface of the lungs is covered with a serous membrane known as visceral pleura (VP). It consists of a simple squamous mesothelium (SS) and underlying connective tissue (CT). Pulmonary alveoli (A) are seen deep to the pleura. *(X250)*



NASAL EPITHELIUM Respiratory epithelium (RE) is a PSCC with goblet cells. It lines most of the nasal cavity as well as the trachea and bronchi. In the superior portion of the nasal cavity, the typical respiratory epithelium is replaced by olfactory epithelium (OE), identifiable by its thickness and lack of goblet cells. An arrow marks the junction of the two epithelia. The vascular lamina propria (LP) is deep to the epithelium. *(X210)*

EPIGLOTTIS The epiglottis projects over the larynx and prevents food from going down it during swallowing. The superior and anterior portion is lined with nonkeratinized stratified squamous (SS), as shown here. Mucous and serous glands (G) may be seen in the lamina propria (LP). Internally, there is a leaf-shaped piece of elastic cartilage (EC) surrounded by a perichondrium (P). *(X20)*

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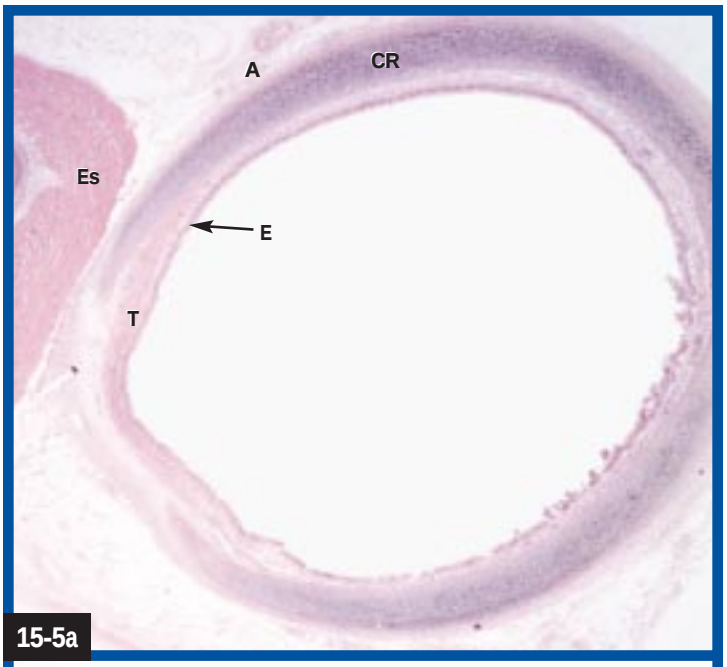
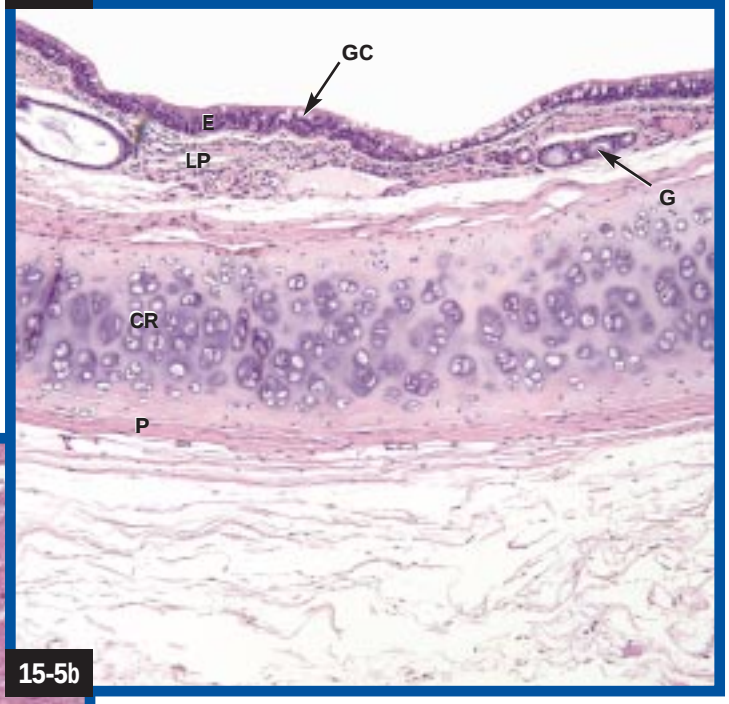
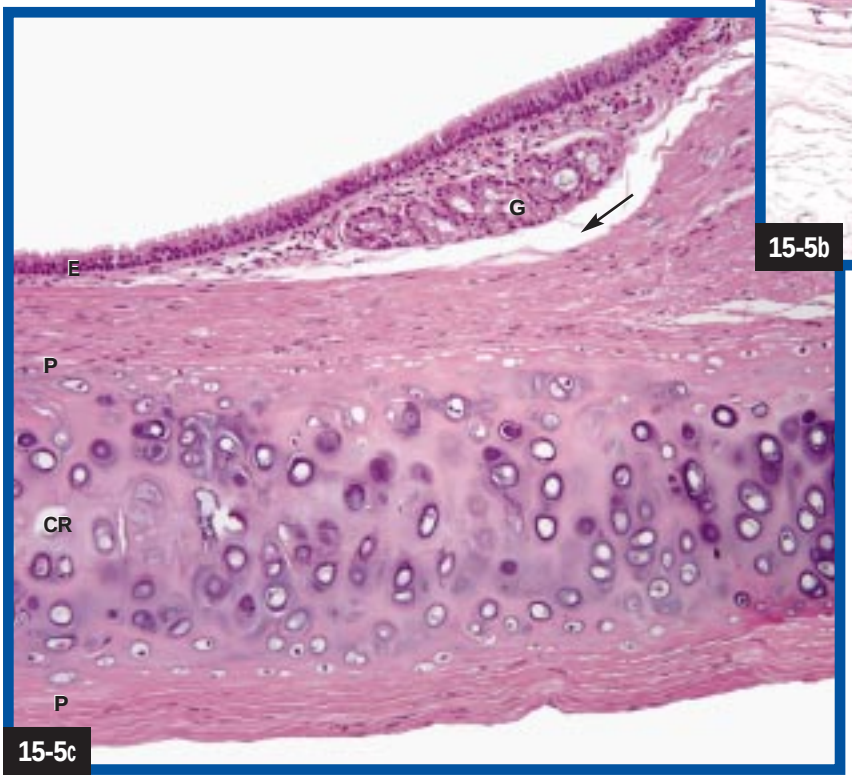
VOCAL FOLD The true vocal folds (VF) in the larynx are responsible for sound production. Each (one is shown here) is lined with non-keratinized stratified squamous epithelium (SS) and has the vocal ligament (VL) and vocalis muscle (VM) within. The space above is the ventricle (V). *(X50)*







TRACHEA The tracheal mucosa is a PSCC (E) with a loose connective tissue lamina propria (LP). Tracheal glands (G) may be present in the submucosa. C-shaped cartilagenous rings (CR) made of hyaline cartilage and covered by a perichondrium (P) provide structural support and are found in the fibrous adventitia (A). The rings are positioned with their open side toward the esophagus (Es). Their ends are joined by the trachealis muscle (T). (a) The entire trachea is shown in this micrograph. The esophagus is toward the left. (*X20*) (b) In this micrograph, the light staining goblet cells (GC) in the PSCC are just barely visible. (*X50*) (c) Mucous secreting tracheal glands are seen in the submucosa of this specimen. The space indicated by the arrow is a preparation artifact. *(X125)*

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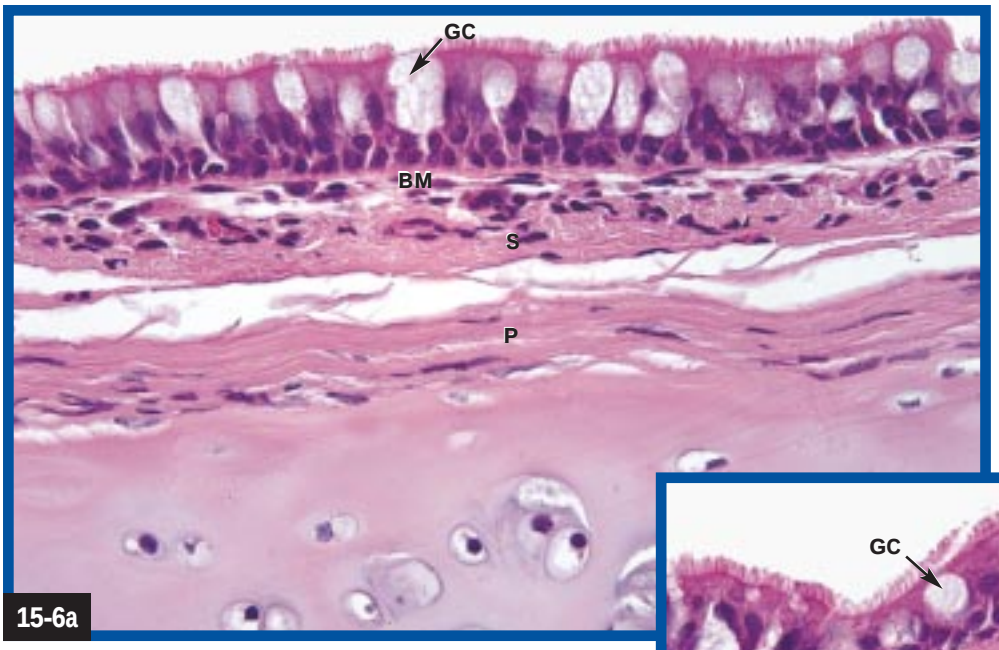
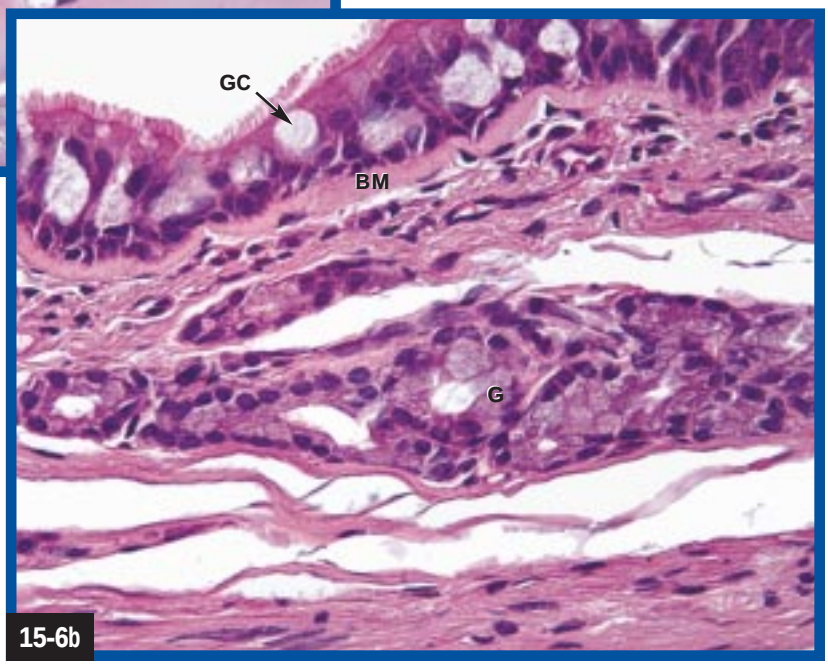
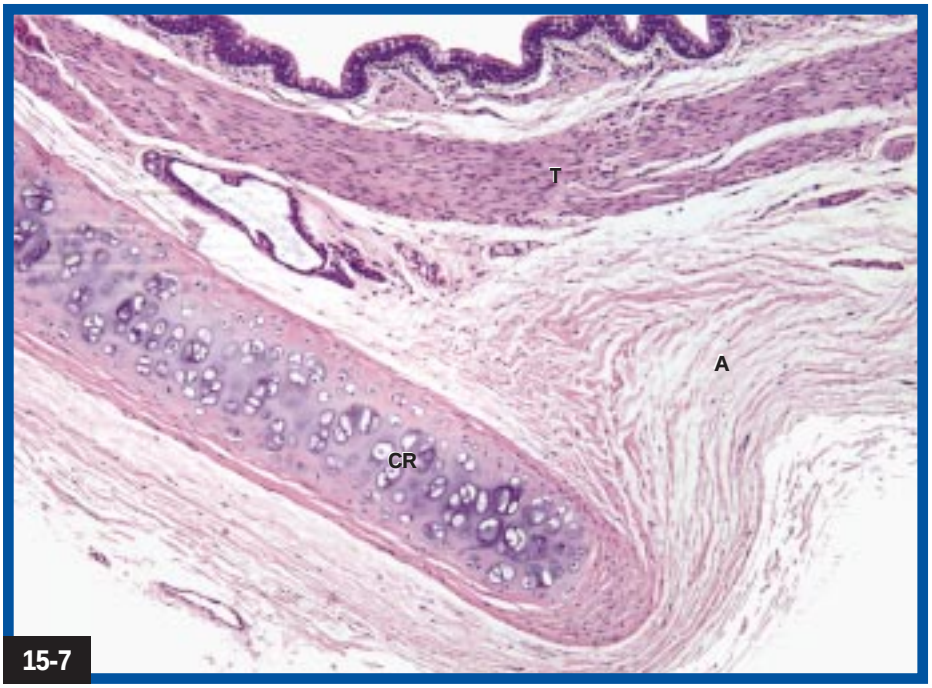




TRACHEAL MUCOSA The PSCC with goblet cells (GC) is characteristic of respiratory epithelium. Note the thick basement membrane (BM) in both micrographs. (a) In this specimen, there is very little lamina propria and submucosa between the mucosa and the hyaline cartilage. In fact, if it weren't for the fact that they are separated, it would be difficult to distinguish the perichondrium (P) from the submucosa (S). (b) A tracheal gland (G) is visible in this micrograph. Both micrographs are X380.



TRACHEALIS MUSCLE The trachealis muscle (T) is smooth muscle that joins the ends of the C-shaped rings in the trachea. The adventitia (A) and hyaline cartilage ring (CR) are also visible. *(X65)*

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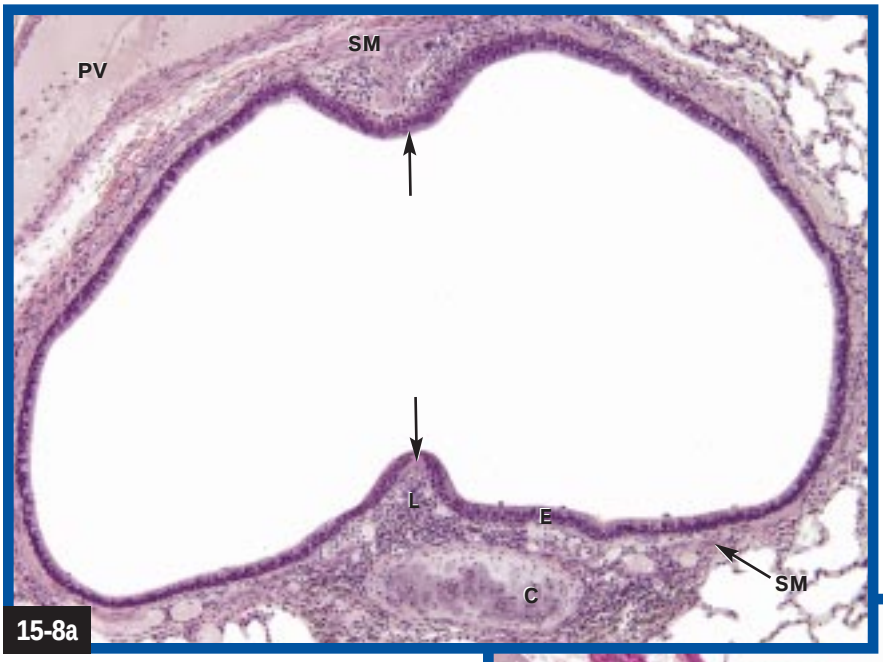

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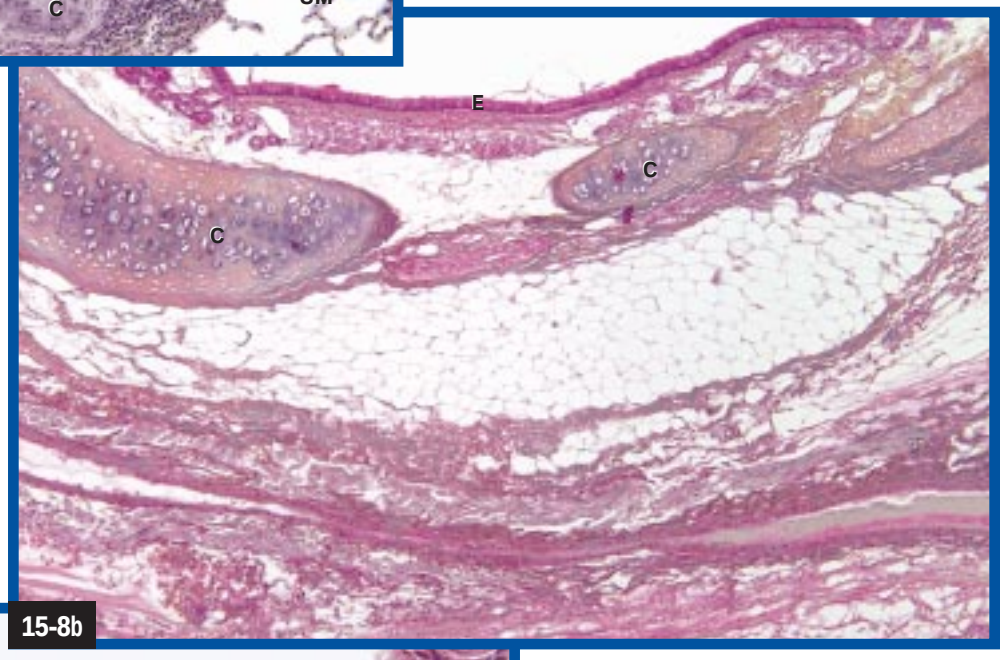

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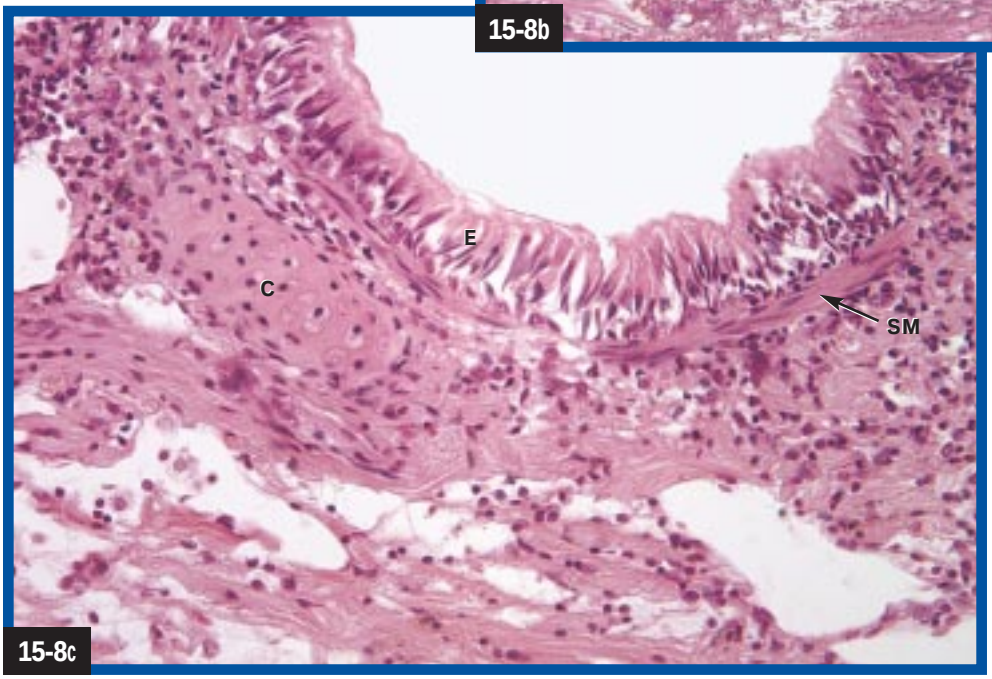

15-8c

BRONCHI Bronchi are the first generations of branches off the trachea and have a similar construction. The plate-like cartilages (C) and thinner epithelium (E) are the main differences. (a) This specimen has only a single cartilage at the plane of section and it does not encircle the bronchus—it is plate-like. Note the smooth muscle (SM) and the lymphatic tissue (L) in the submucosa. Also seen is a branch of the pulmonary vein (PV). As a side note, this section was made near a point of bifurcation, as evidenced by the indentations of the bronchial wall into the lumen (arrows). (*X50*) (b) More plates of cartilage are seen in this specimen, indicating it is from a larger bronchus than in (a). (*X50*) (c) Smooth muscle and one piece of cartilage are visible in this specimen. *(X250)*

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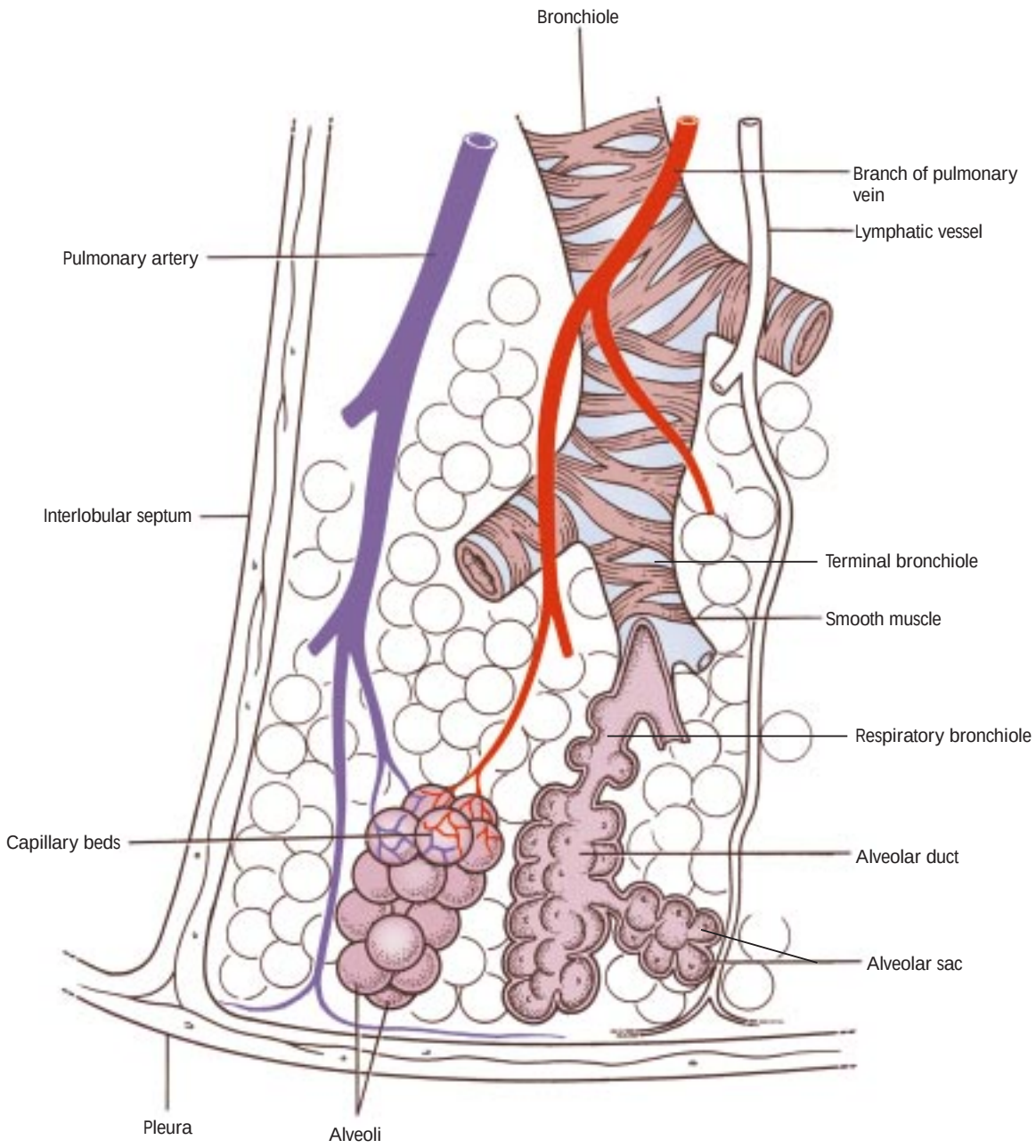

15-9

RESPIRATORY TREE The final few branches of the respiratory tree are shown in this illustration. Terminal bronchioles represent the end of the conducting portion of the respiratory tree. Beyond these, all components belong to the respiratory portion because they have alveoli and are involved in gas exchange.

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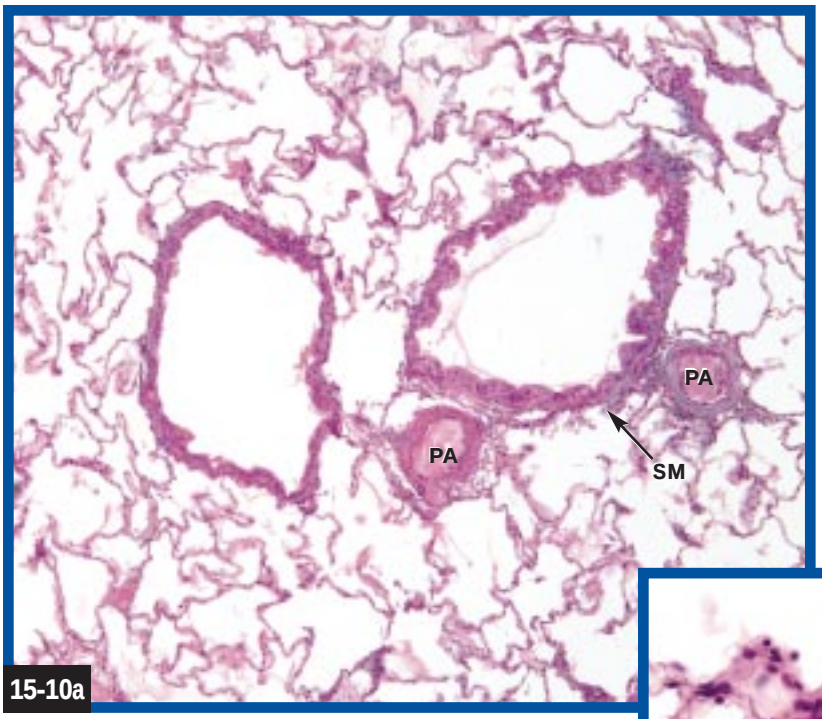

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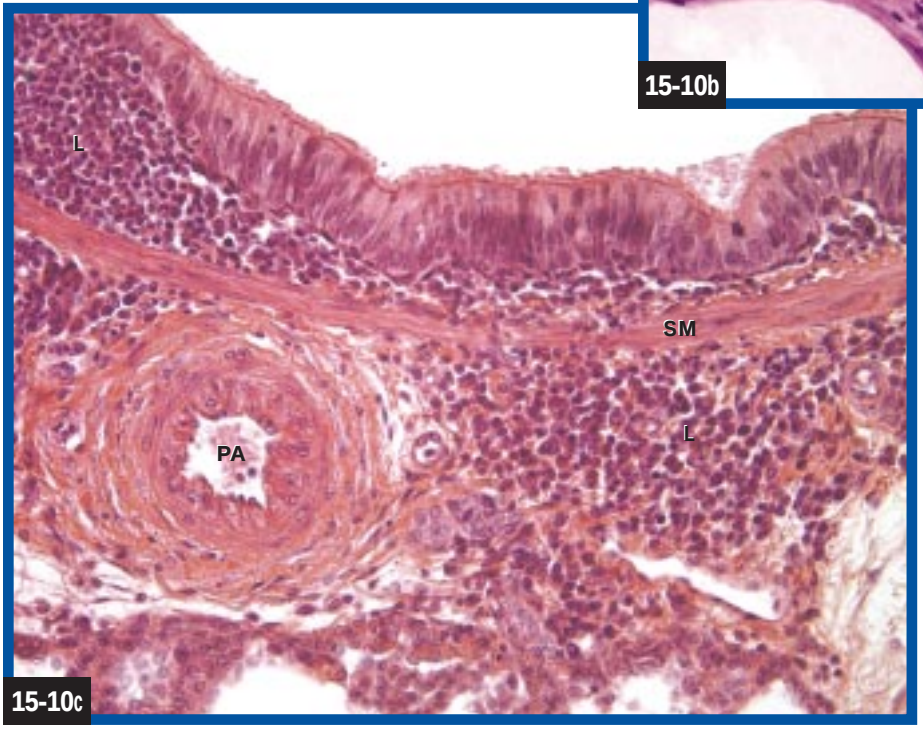

15-10c

BRONCHIOLES Bronchioles are only found within the lung and maintain the general appearance of the bronchi, only smaller. The absence of cartilage distinguishes them from bronchi. The epithelium ranges from low PSCC to simple ciliated columnar. Smooth muscle is present. (a) The mucosa of these bronchioles is folded, a result of the smooth muscle (SM) in the wall and the absence of cartilage. Notice the lung tissue around the bronchioles and the two branches of the pulmonary artery (PA). (*X65*) (b) This bronchiole is lined with a simple ciliated columnar (CC) epithelium lacking goblet cells. A few dome-shaped and nonciliated Clara cells (C) are present. Notice the thin lamina propria (LP) and small amount of smooth muscle in the wall (SM). (*X250*) (c) Lymphatic tissue (L) and smooth muscle (SM) are seen in this bronchiole. Based on the PSCC epithelium, it can be concluded that this bronchiole is larger than the specimen in (b) even though only a portion of it is shown. Notice the small branch of the pulmonary artery (PA). *(X230)*

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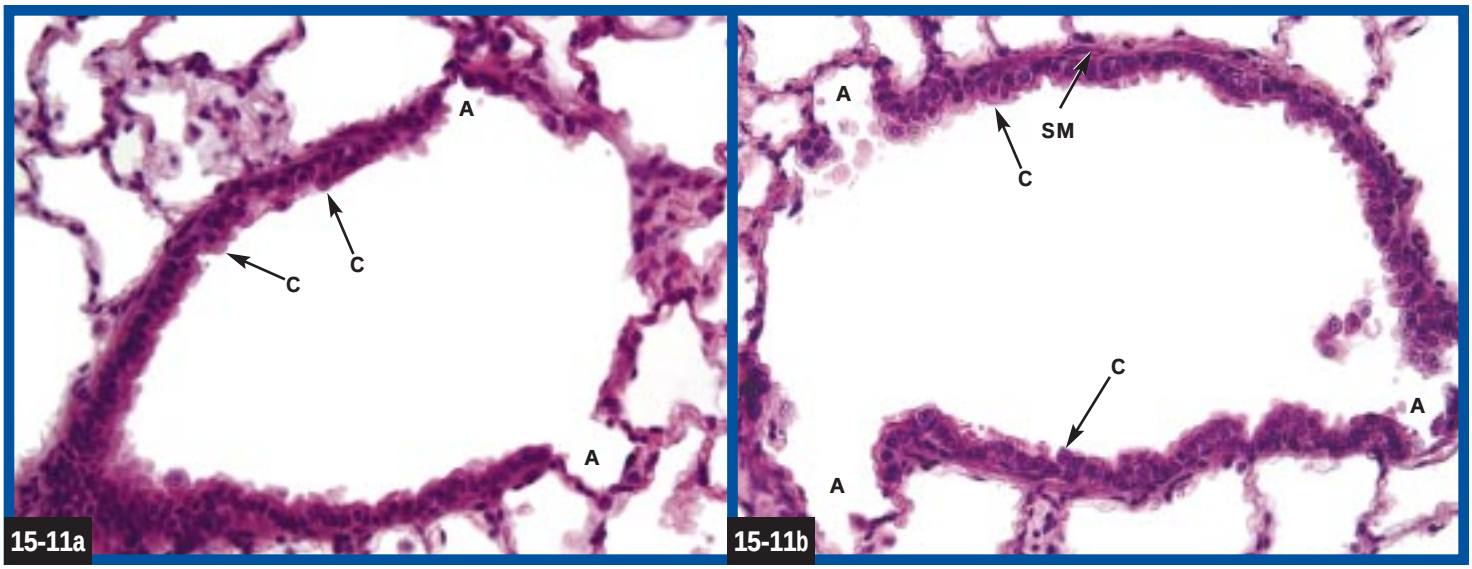
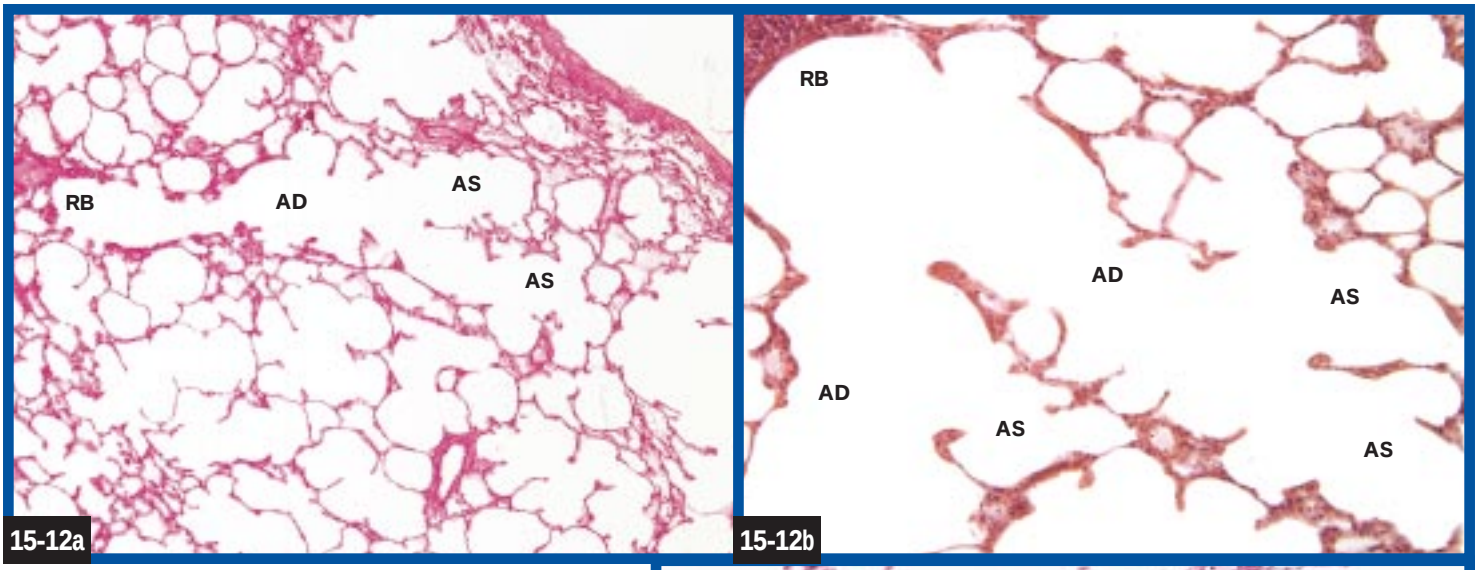
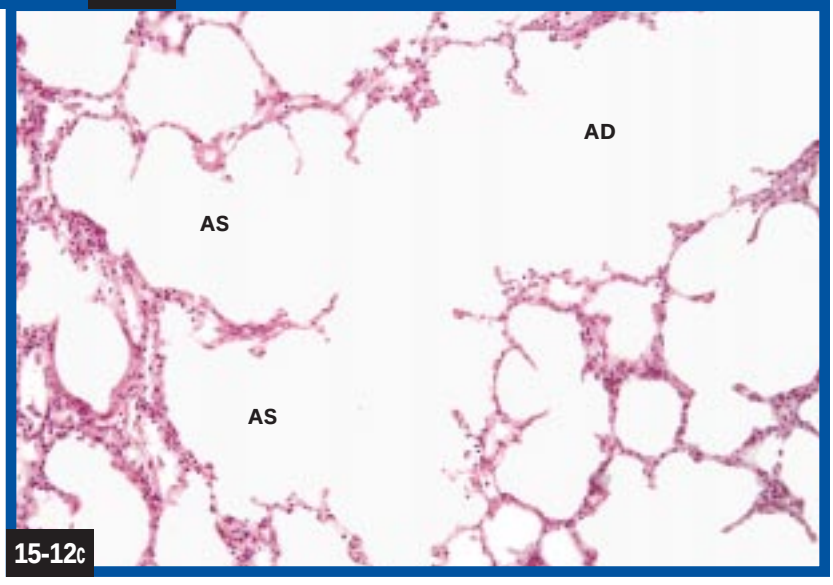


RESPIRATORY BRONCHIOLES Respiratory bronchioles resemble terminal bronchioles in structure except for the alveoli (A) in their walls. Clara cells (C) are present in the simple cuboidal epithelium. Only a few of the epithelial cells are ciliated. A thin layer of smooth muscle (SM) is also visible. Both micrographs are X210.





ALVEOLAR DUCTS Each respiratory bronchiole (RB) leads to an alveolar duct (AD), a passage made of alveoli (A) that terminates in alveolar sacs (AS). (a) In this micrograph, a respiratory bronchiole (RB) is seen to lead into an alveolar duct and two (in this plane of section) alveolar sacs. (*X50*) (b) This micrograph shows a respiratory bronchiole branching into two alveolar ducts. (*X110*) (c) Here is another example of an alveolar duct and alveolar sacs. It takes some searching of lung specimens to find examples cut in the proper plane to illustrate the branching, so don't be discouraged if you don't see one right away. (*X110*)

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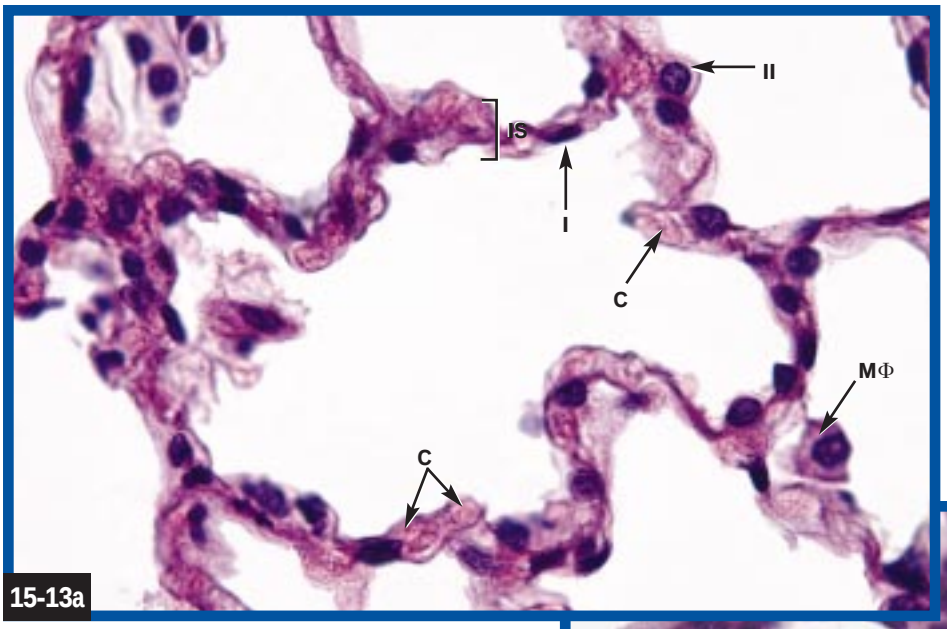

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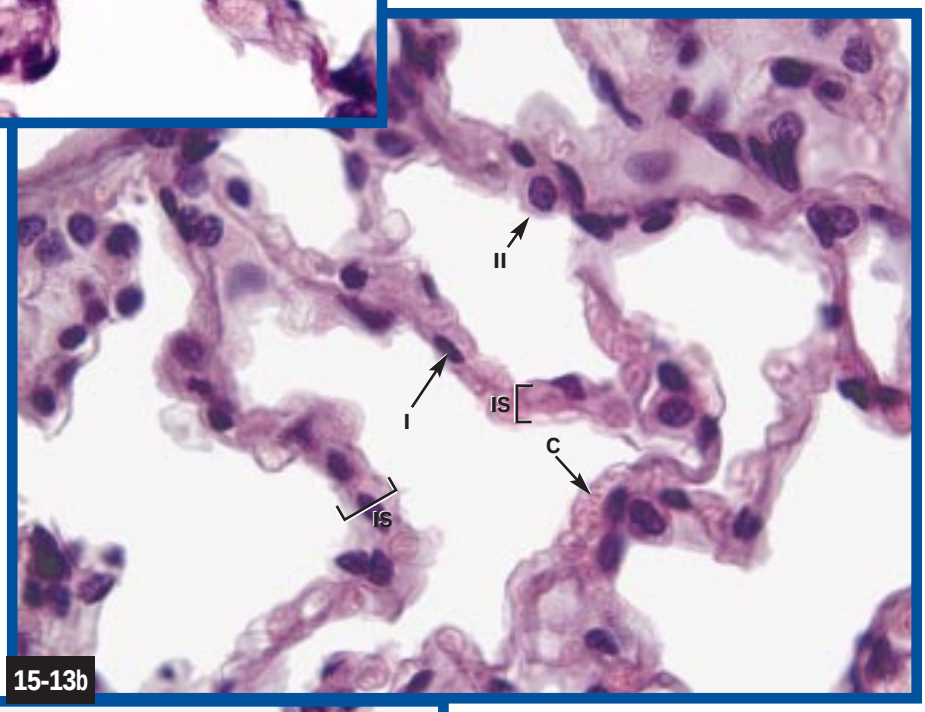
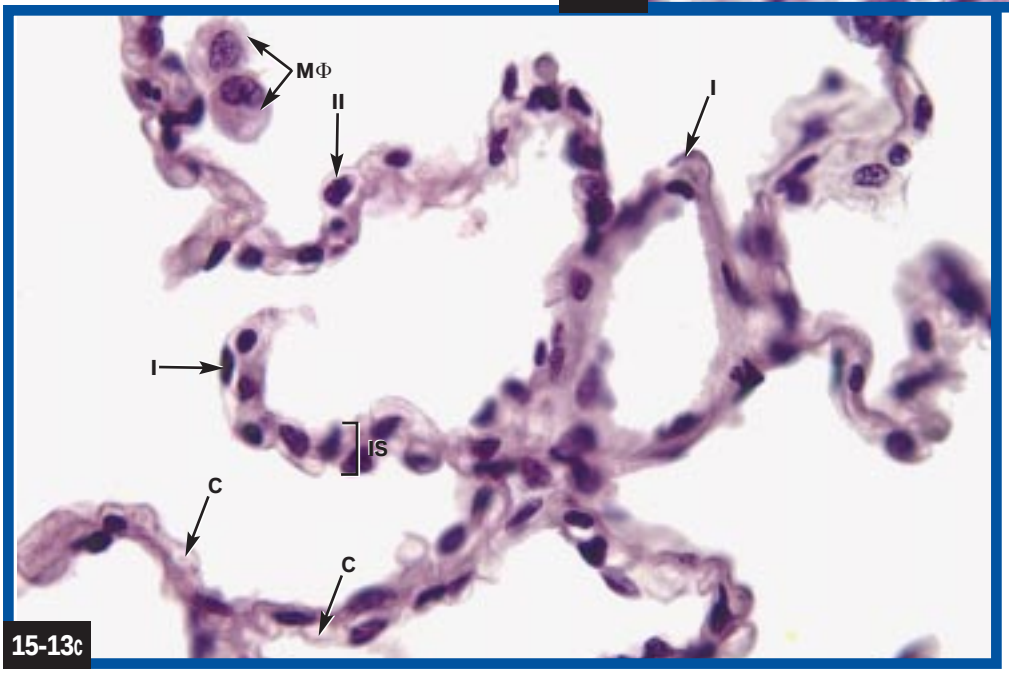


15-13b

ALVEOLI Each alveolus is lined by a simple squamous epithelium that is difficult to see clearly in standard preparations. More easily seen are the interalveolar septa (IS) formed from the epithelia of neighboring alveoli, plus capillaries (C) and a small amount of elastic connective tissue between them. The alveolar epithelium is composed of simple squamous Type I pneumocytes (I) and the cuboidal Type II pneumocytes (II). Alveolar macrophages (MΦ) may be seen in the interalveolar septa or free in the alveolar spaces. All micrographs are X630.



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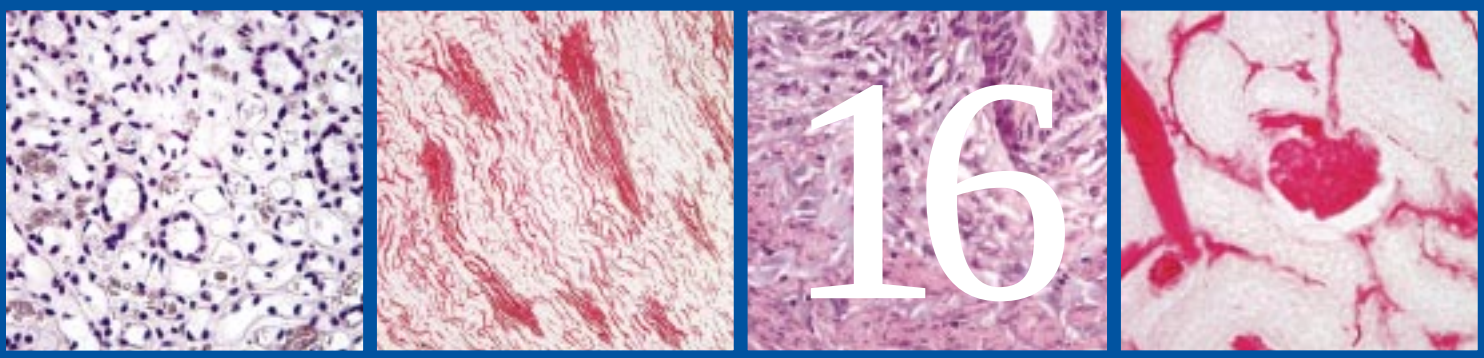
Urinary System

CHAPTER 16



Introduction

The organs of the urinary system are the two kidneys and ureters, the urinary bladder, and urethra. Its function is to maintain fluid and electrolyte homeostasis by filtering the blood to remove wastes and excess ions, and conserve water and ions that are in short supply. It also is involved in maintaining blood pressure by adjusting blood volume.

Kidneys

The kidneys are paired organs that occupy the retroperitoneal region just inferior to the diaphragm on the dorsal body wall. They are kidney bean in shape (!) and the indentation, called a **hilus**, faces medially. Renal blood vessels, lymphatics, and the ureter enter at the hilus. The **renal pelvis** is a dilation of the ureter's proximal end. It branches to form **major** and **minor calyces** that connect with the apices of the pyramids (see below). A **fibrous capsule** covers the kidney's surface.

Internally, the kidney presents a **renal cortex** and **renal medulla**. In section, the medulla appears as six to 12 triangular and striated regions called **renal pyramids**, which accurately describes their three-dimensional shape. The apex of each pyramid projects into a minor calyx as a **renal papilla** and has approximately twenty openings called **ducts of Bellini**. This forms the **area cribrosa**. The base of each pyramid is adjacent to the cortex. The cortex has a granular appearance and occupies the outer portion of the kidney, forming the **cortical arch**. Thin extensions of medullary tissue into the cortical arch are called **medullary rays**. **Cortical columns** are found between the pyramids.

Uriniferous tubules constitute the functional units of the kidneys. Each tubule is composed of a **nephron** and a **collecting tubule**, though the latter are shared by many nephrons. Collecting tubules converge to form the ducts of Bellini.

There are approximately 1.3 million nephrons in each kidney. Each nephron consists of a renal corpuscle (Bowman's capsule and glomerulus—see below), proximal convoluted tubule, loop of Henle, and distal convoluted tubule (Figure 16-1). **Cortical nephrons** are located in the cortex, with their loops of Henle barely penetrating the medulla. **Juxtamedullary nephrons** are located near the junction of the cortex and medulla. They have long loops of Henle that penetrate deep into the medulla.

The oval **renal corpuscles** (Figure 16-2) are the site of blood filtration. They are located in the cortex and are quite complex in structure. Each is composed of a capillary tuft called a **glomerulus**, which is surrounded by a **Bowman's capsule**. The glomerulus is made of an endothelium with fenestrations up to 100 nm in diameter. A three-layered **basal lamina** is deep to the endothelial cells and contributes to the filtration mechanism.

During development, the glomerulus pushes into the dilated and spherical Bowman's capsule at the proximal end of the nephron, not unlike a fist pushing into a deflated playground ball and collapsing it upon itself. The outer layer of Bowman's capsule, the **parietal layer**, is a simple squamous epithelium. The inner layer, which is in contact with the glomerular capillaries, is called the **visceral layer** and is composed of cells called podocytes (Figure 16-3).

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Podocyte processes wrap around the glomerular capillaries, but leave small gaps about 25 nm in width called **filtration slits**.

Blood enters the glomerulus through the **afferent arteriole** and leaves through the **efferent arteriole**, both of which penetrate the renal corpuscle at its **vascular pole** (Figure 16-4). The afferent arteriole is larger than the efferent arteriole, resulting in resistance to blood flow. The pressure produced by this size difference forces fluid and molecules smaller than a molecular weight of 65,0000 daltons from the blood through the filtration slits and basal lamina, and into the interior of Bowman's capsule, **Bowman's space**. The fluid is called glomerular ultrafiltrate. In healthy kidneys, blood cells and large molecules are absent from the ultrafiltrate.

Intraglomerular mesangial cells are associated with the glomerulus and are phagocytic in function. Their primary role is to remove molecules trapped on the basal lamina that would impede filtration if they weren't removed. They are also contractile and adjust blood flow through the glomerulus. **Extraglomerular mesangial cells** are located at the vascular pole.

Emerging from the **urinary pole** of the renal corpuscle is the **proximal tubule**, whose lumen is continuous with Bowman's space (Figure 16-5). The epithelium is simple cuboidal with a brush border and a prominent basal lamina, demonstrable with a PAS stain. In most paraffin preparations, the lumen is closed. Juxtamedullary nephrons have two parts to the proximal tubule: The tortuous **proximal convoluted tubule (pars convoluta)** in the cortex, and the straight **descending thick limb of Henle's loop (pars recta)** in medullary rays. Up to 80% of the sodium, chloride, and water is reabsorbed in the proximal tubule and returned to the blood, as are all the glucose and amino acids in the ultrafiltrate.

The **descending thin segment of Henle's loop** is a continuation of the thick segment (Figure 16-6). It passes into the medulla where it makes a hairpin turn called **Henle's loop**, and continues back to the cortex as the **ascending thin segment of Henle's loop**. All parts are lined with a simple squamous epithelium. The thin limbs resemble capillaries (which are also present—see page 189) except for their thicker epithelial cells with less dense staining nuclei and absence of red blood cells within. Henle's loop is involved in a countercurrent mechanism for concentration of the urine; it establishes the range of osmolarities for final urine concentration. This is accomplished, in part, by the relative impermeability to water by the ascending limb.

The ascending limb of Henle's loop continues as the **distal tubule**. It is composed of an **ascending thick limb of Henle's loop (pars recta)**, the **macula densa**, and the **distal convoluted tubule (pars convoluta)**. A simple cuboidal epithelium lines the distal tubule, which is in the cortex (Figure 16-7). The distal tubule passes between its own afferent and efferent arterioles. This portion is called the **macula densa** and is characterized by narrower cells. The pars convoluta is tortuous but shorter than its proximal counterpart (and therefore less abundant in sections of renal cortex). The cells are paler staining with round, apical nuclei and prominent nucleoli, and the lumen is typically open. The distal tubule is impermeable to water and urea, which contributes to the mechanism of urine concentration. In addition, a sodium-potassium pump reclaims sodium from the urine in response to the hormone aldosterone from the adrenal cortex, and excess hydrogen and potassium ions are pumped into the lumen.

The **juxtaglomerular (JG) apparatus** (Figure 16-8) is formed from the macula densa, **juxtaglomerular (JG) cells** in the tunica media of the afferent arteriole (and sometimes the efferent arteriole) and the extraglomerular mesangial cells. The basal lamina is absent from the macula densa cells, so they are in direct contact with the JG cells. The JG apparatus is involved in maintaining blood pressure via two separate mechanisms. First, if the macula densa cells detect a low sodium concentration, they cause dilation of the afferent arteriole, which increases intraglomerular pressure. Second, they stimulate the JG cells to release renin into the blood. Renin activates the angiotensin system, which causes vasoconstriction and increases blood pressure. It also stimulates the adrenal cortex to release aldosterone, resulting in greater sodium resorption and an increase in blood volume, which also increases blood pressure.

The distal convoluted tubules of several nephrons empty into a **collecting tubule**, which is not considered part of the nephron. **Cortical collecting tubules** have a simple cuboidal epithelium and are located in the medullary rays (Figure 16-9). They are involved in acid-base homeostasis through secretion of hydrogen ions. Cortical collecting tubules join to form **medullary collecting tubules**, which also have a simple cuboidal epithelium but are located in the pyramids. These join and form **papillary collecting tubules** (ducts of Bellini) (Figure 16-10) that empty into a minor calyx at the renal papilla. All collecting tubules are impermeable to water, but their permeability is increased in the presence of antidiuretic hormone (ADH); the more ADH, the more water leaves the tubule, and the more concentrated the urine becomes.

Renal Circulation and the Renal Interstitium

Normally, gross circulation is not in the domain of histology, but often the following blood vessels are identifiable in kidney sections. Blood enters the kidney through the renal artery at the hilus. The renal artery branches into segmental arteries, lobar arteries, interlobar arteries (found next to the pyramids), arcuate arteries (found along the base of pyramids), and interlobular arteries (which go into the cortical

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arch between medullary rays). Several afferent arterioles branch off the interlobular arteries, empty into the glomerulus, which is drained by the efferent arteriole. **Peritubular capillaries** (for cortical nephrons) and **vasa recta** (for juxtaglomerular nephrons) arise from the efferent arteriole and form a plexus around the convoluted tubules and loop of Henle, respectively (Figure 16-11). These extensive capillary networks pick up materials that have left the renal tubule as a result of active transport, osmosis, or diffusion. Thus, useful materials that left the blood as ultrafiltrate are returned to the blood.

Arcuate veins drain the capillaries. The veins leading out of the kidney follow the arteries coming in, and have the same names (with the exception of lobar and segmental veins, which are absent).

All blood vessels in the kidney are found in the **renal interstitium**, the region between the tubules. It is composed of a small amount of fibrous connective tissue with fibroblasts, macrophages, and interstitial cells.

Calyces and Renal Pelvis

Each renal papilla projects into a minor calyx. Minor calyces combine to form three or four major calyces, which in turn empty into the renal pelvis. All are lined with a transitional epithelium and lamina propria. A thin smooth muscle layer is deep to the lamina propria and is responsible for moving urine toward the ureters.

Ureters

The ureters are 25 to 30 cm long and 4 mm in diameter. They pass along the dorsal body wall and enter the posterior and inferior aspect of the urinary bladder. Each is composed of three layers: mucosa, muscularis, and adventitia (Figure 16-12).

The **mucosa** is made of a transitional epithelium and a dense irregular connective tissue in the **lamina propria**. Deep to this is the **muscularis** made of two smooth muscle layers: an inner **longitudinal layer** and an **outer circular layer**. Note that the arrangement is just the opposite of the muscularis layers in the digestive tube, but the function is the same; that is, peristalsis. In the distal third of the ureter, an additional layer of longitudinal muscle is added on the surface of the circular layer. The outermost layer is the fibrous **adventitia**, which blends with the renal capsule and the adventitia of the urinary bladder.

Urinary Bladder

The **urinary bladder** stores urine until micturition. A smooth, triangular region called the **trigone** is formed where the two ureters enter and the urethra leaves.

There are three layers in the urinary bladder wall (Figure 16-13). These are the mucosa, muscularis, and adventitia or serosa. The **mucosa** consists of a transitional epithelium and a **lamina propria** made of a superficial dense connective tissue and a deeper loose connective tissue. The epithelium is an osmotic barrier, preventing water from the bladder's wall entering the hyperosmotic urine. In the empty bladder, the mucosa demonstrates nonpermanent folds called **rugae** (except at the trigone). These flatten as the bladder fills.

Three loosely organized layers of smooth muscle form the **muscularis**. These correspond to the layers seen in the distal ureter. That is, an **inner longitudinal layer**, **middle circular layer**, and an **outer longitudinal layer**, but these are often difficult to identify. The circular layer is thicker at the **internal urethral orifice** where it forms the **internal urinary sphincter**. A dense irregular connective tissue comprises the **adventitia**, which covers most of the organ. The superior aspect of the bladder is covered with a **serosa**, the parietal peritoneum.

Urethra

The **urethra** carries urine from the bladder to the external environment. As the urethra penetrates the **urogenital diaphragm**, a ring of skeletal muscle acts as the voluntary **external urinary sphincter**.

The **female urethra** (Figure 16-14) is about 5 cm long and 6 mm in diameter, and the **external urethral orifice** opens into the vestibule of the vagina. The **mucosa** presents longitudinal folds and is mostly lined with nonkeratinized stratified squamous epithelium with occasional patches of PSCC. **Glands of Littré**, found in the **lamina propria**, secrete mucus to lubricate the mucosa. An **inner longitudinal layer** and an **outer circular layer** of smooth muscle comprise the **muscularis**. The muscularis is surrounded by skeletal muscle at the external urinary sphincter.

The **male urethra** (Figure 16-15) is longer than the female urethra, being up to 20 cm in length. It is divided into three segments based on location. These are the prostatic urethra, membranous urethra, and spongy (penile) urethra.

The **prostatic urethra**, lined with transitional epithelium, passes through the prostate gland. The microscopic prostatic ducts and the two ejaculatory ducts empty into it. The **membranous urethra** passes through the urogenital diaphragm. Its epithelium is stratified columnar with occasional regions of PSCC. This segment is the site of the external urinary sphincter. The **spongy (penile) urethra** passes through the **corpus spongiosum** of the penis and leads to the **external urethral orifice** at the end of the **glans penis**. Most of its length is lined with stratified columnar or PSCC epithelium with stratified squamous at the orifice.

As with the female, numerous **glands of Littré** are present in the lamina propria of all segments.

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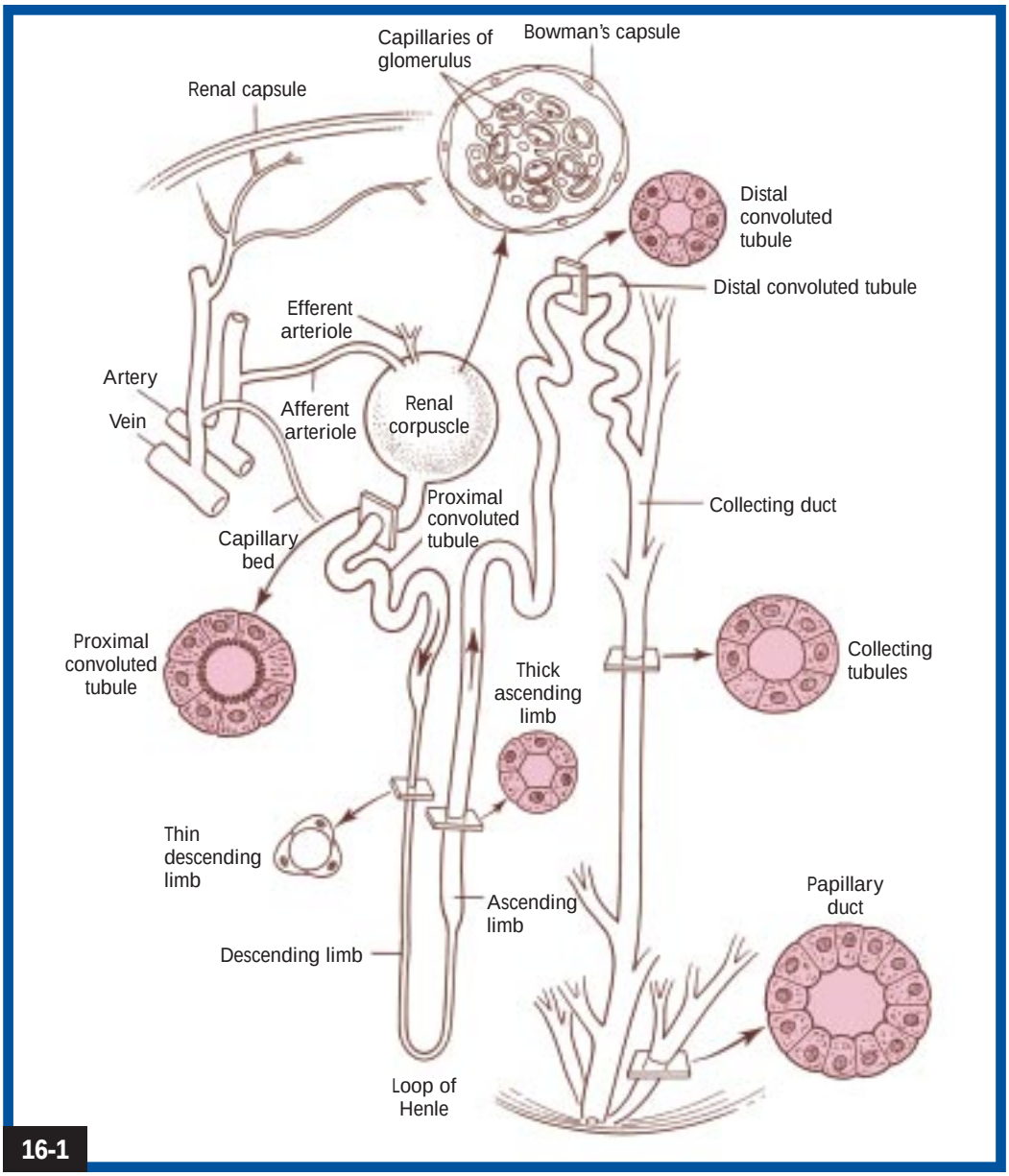
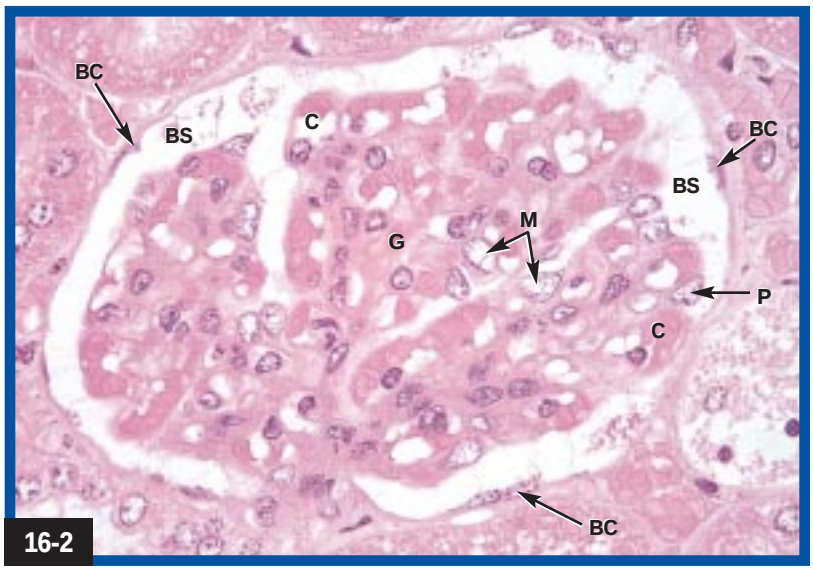


THE NEPHRON Shown is an artist's rendition of a juxtamedullary nephron.



RENAL CORPUSCLE Renal corpuscles consist of a glomerulus (G) surrounded by a Bowman's capsule. The parietal layer of Bowman's capsule (BC) is a simple squamous epithelium and lines Bowman's space (BS). The glomerular capillaries (C), podocytes (P), and mesangial cells (M) can be difficult to sort out in some preparations, but are visible in this specimen. *(X530)*

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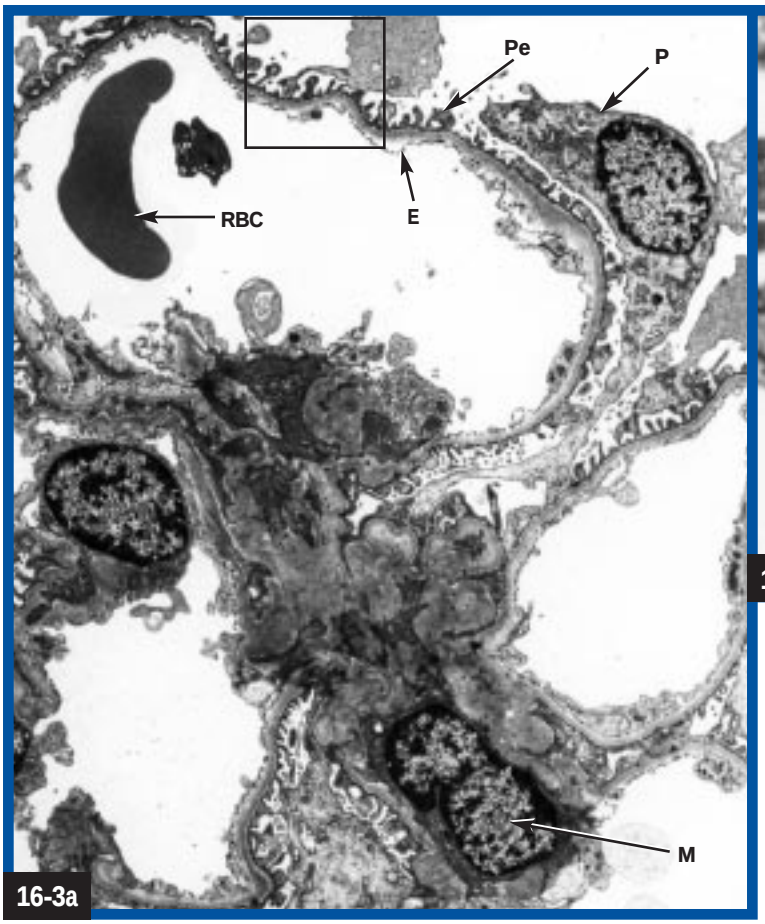
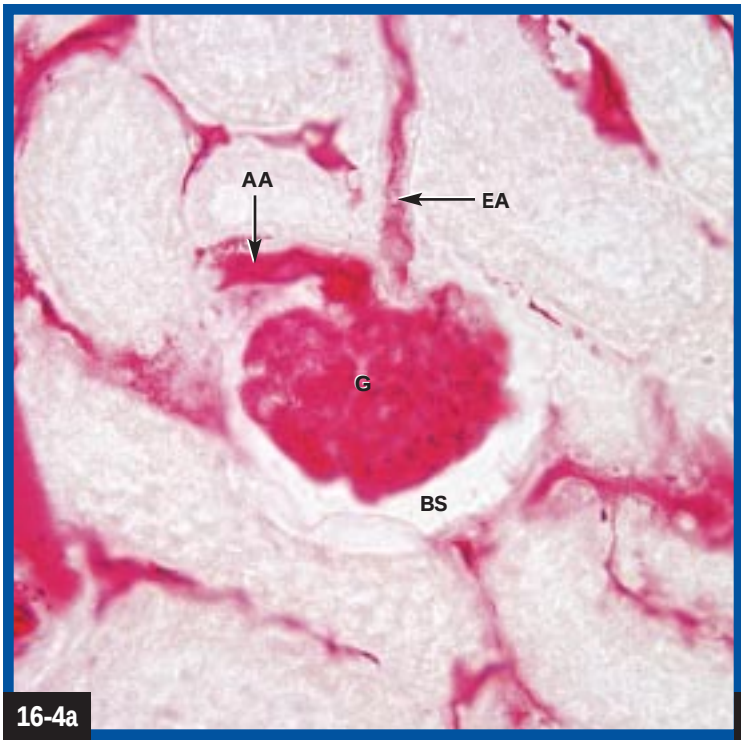
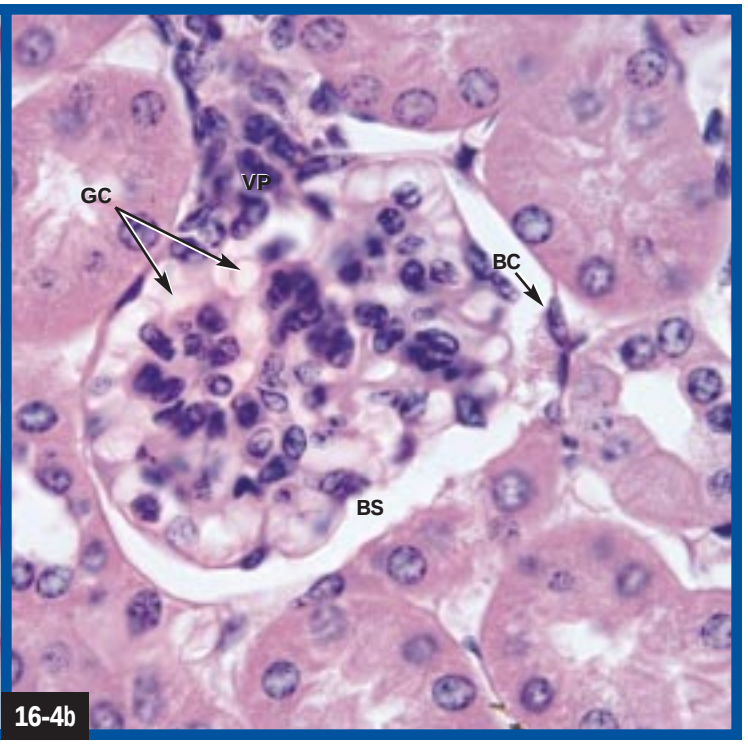


ELECTRON MICROGRAPH OF A GLOMERULUS (a) Visible in this micrograph is a podocyte (P) with pedicels (Pe) on the endothelium (E) of a glomerular capillary. An RBC and a mesangial cell (M) are also visible. (*X3700*) (b) This is an enlargement of the boxed area in (a). The gaps between pedicels (Pe) and the capillary fenestrations (F) are visible, as is the three-layered basal lamina (BL). (*X18,500*)
(Courtesy of UCSD Medical Center.)





AFFERENT AND EFFERENT ARTERIOLES (a) In this micrograph, the blood vessels have been injected with a red dye. Notice the afferent arteriole (AA) has a larger diameter than the efferent arteriole (EA) emerging from the glomerulus (G). Bowman's space (BS) is also visible though the details of Bowman's capsule are not. *(X380)* (b) In standard sections, the vascular pole (VP) of the renal corpuscle is often visible, but it is difficult to distinguish between the afferent and efferent arterioles. Glomerular capillaries (GC) with blood cells and the parietal layer of Bowman's capsule (BC) are visible, however. *(X680)*

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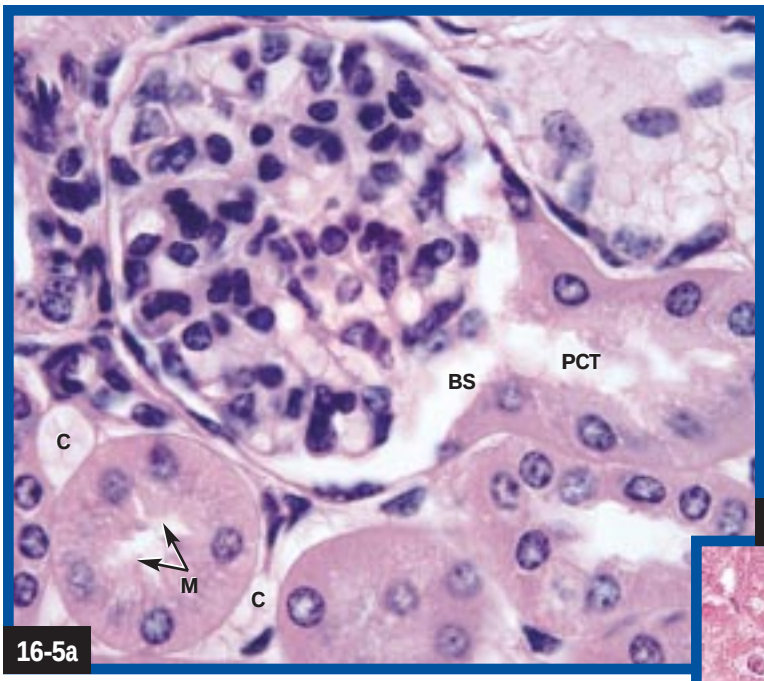
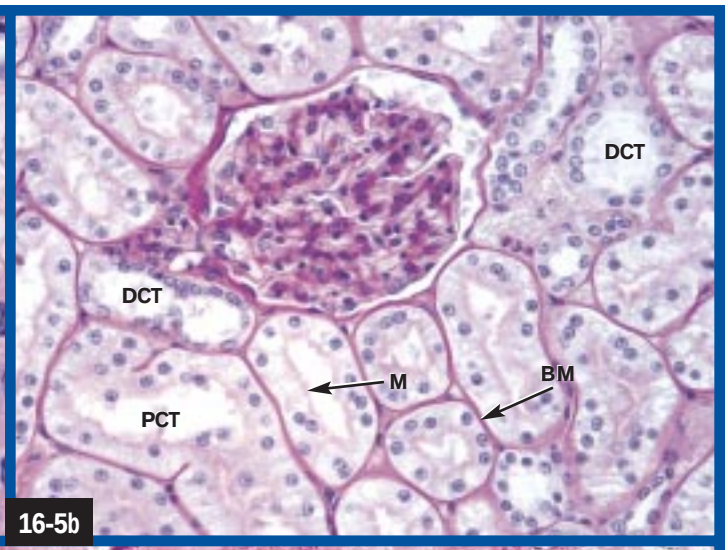
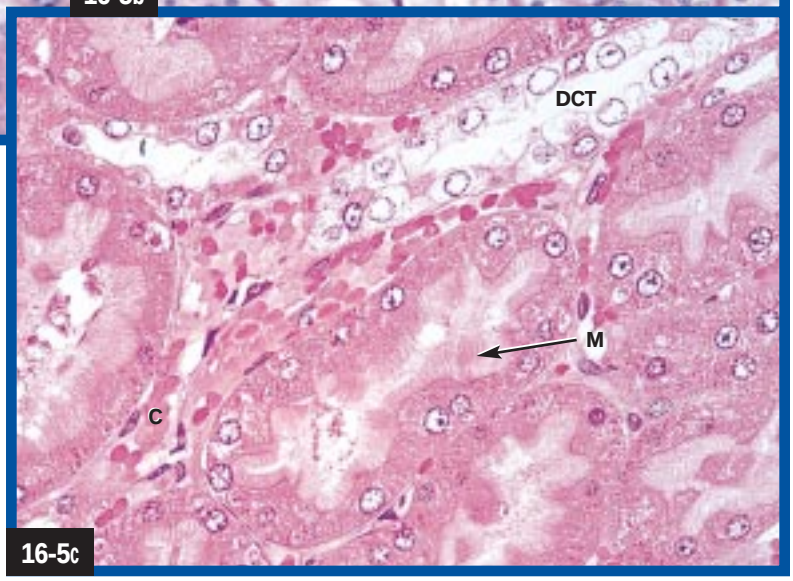
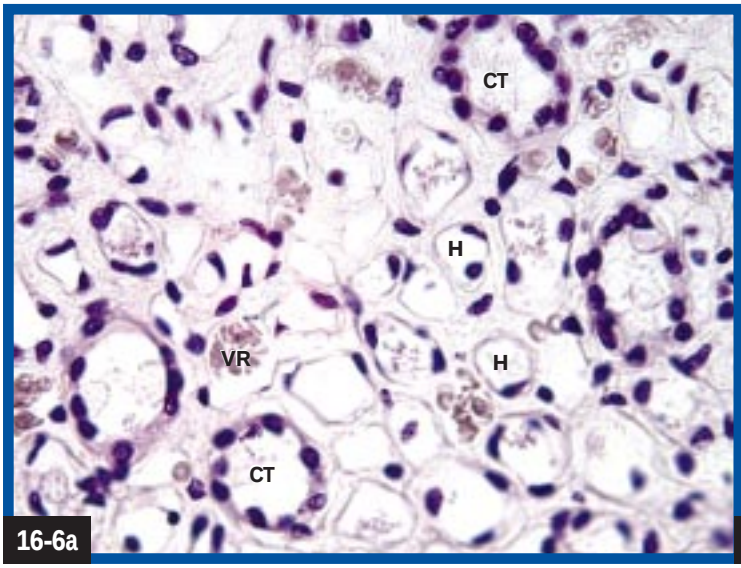
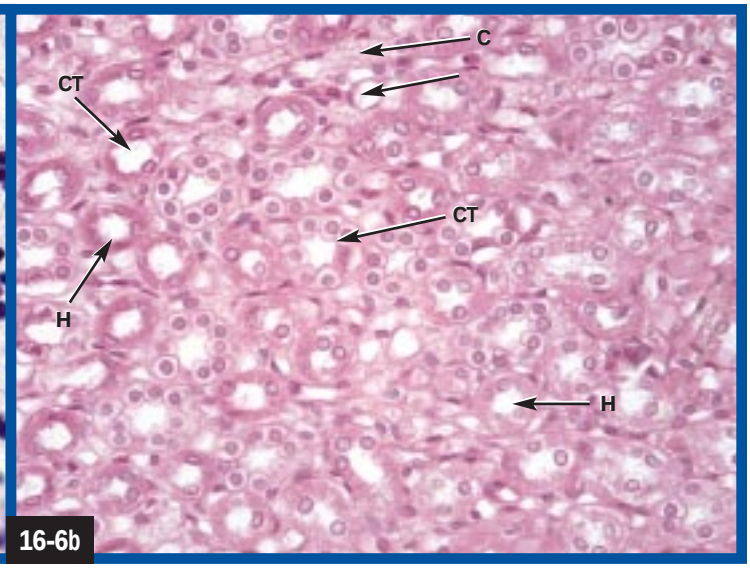






PROXIMAL CONVOLUTED TUBULE (a) The lumen of a proximal convoluted tubule (PCT) is continuous with Bowman's space (BS). Proximal tubules have a simple cuboidal epithelium with microvilli (M), barely discernable in this specimen. All the tubules in this field are proximal convoluted tubules. Note the abundant capillaries (C) surrounding the tubules. *(X660)* (b) In this PAS preparation, the basement membranes (BM) are prominently shown, as are the microvilli lining the proximal tubules. Most tubules in the cortex are proximal tubules, but a couple of distal convoluted tubules (DCT) are also identifiable in this specimen by their open lumen and lack of microvilli. (*X260*) (c) The microvilli of proximal convoluted tubules are seen in this micrograph, as are capillaries and a distal convoluted tubule. *(X400)*





RENAL MEDULLA The medulla has thick and thin segments of the ascending and descending limbs of Henle's loop as well as collecting ducts. (a) In this micrograph, thin segments of Henle's loop (H) and collecting tubules (CT) are visible, as are vasa recta (VR) with blood cells in them. *(X660)* (b) In this section of the medulla, thick segments of Henle's loops are more abundant than in (a). Collecting tubules can be differentiated from other tubules by their pale cytoplasm and prominent lateral cell membranes. Capillaries (C) and an occasional thin segment of Henle's loop (arrow) are also visible. *(X265)*

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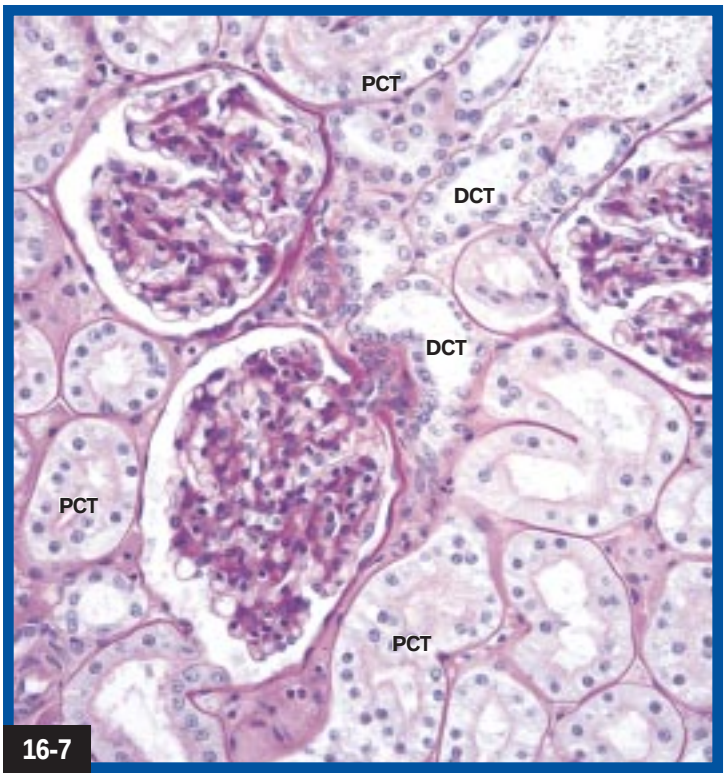
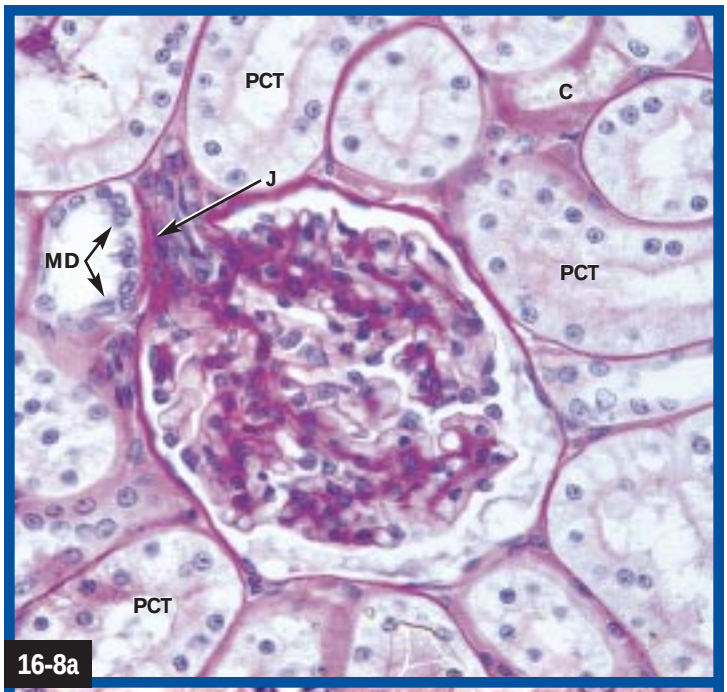
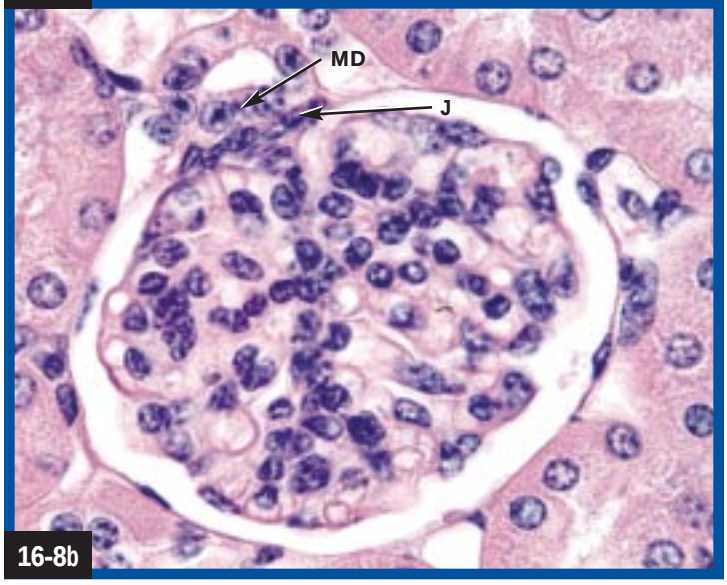
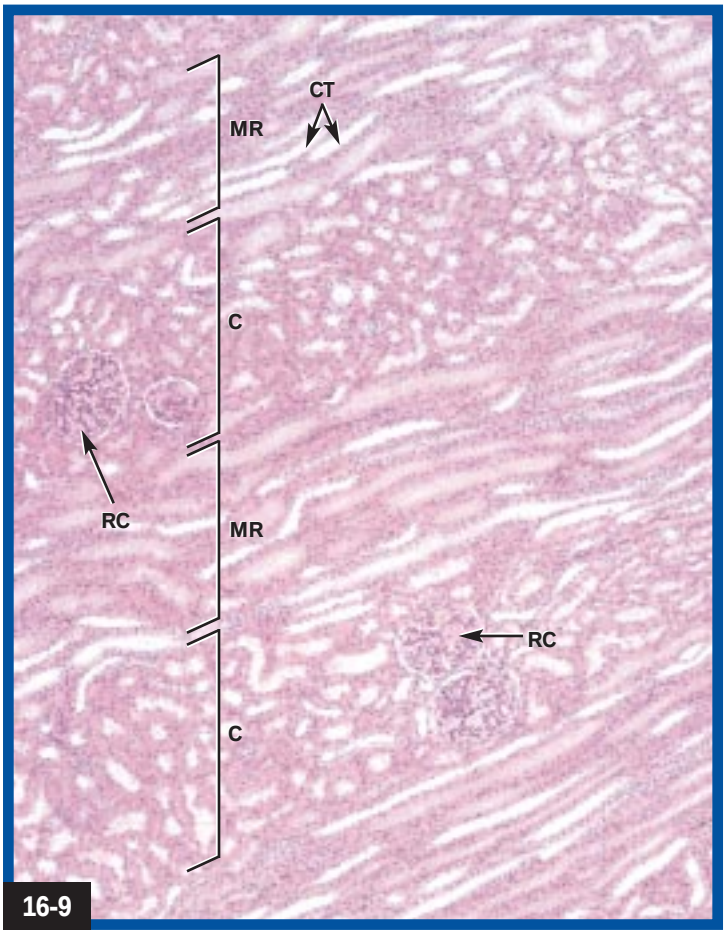


DISTAL CONVOLUTED TUBULE Distal convoluted tubules (DCT) are shorter than proximal tubules (PCT), and so are seen less frequently in sections of renal cortex. Their lumen is more open and they lack microvilli. *(X260)*





JUXTAGLOMERULAR APPARATUS The distal convoluted tubule contacts the afferent (and sometimes the efferent) arteriole at the vascular pole of its renal corpuscle to form the juxtaglomerular apparatus. The arteriole contributes juxtaglomerular cells (J), whereas the distal tubule cells form the macula densa (MD). The macula densa cells are smaller with darker staining nuclei than the other cells of the distal tubule. (a) Note the abundance of proximal tubules (PCT) and the relative scarcity of distal tubules in this specimen. Also notice the capillary (C). (*X365*) (b) The macula densa and juxtaglomerular cells are clearly evident in this micrograph. Note that the distal tubule of the JG apparatus is the only one in the field. *(X610)*



MEDULLARY RAY Medullary tissue is found in the subcapsular cortex as medullary rays (MR). They are easily distinguished from the cortex (C) by the absence of renal corpuscles (RC). The rays contain cortical collecting tubules (CT). *(X65)*

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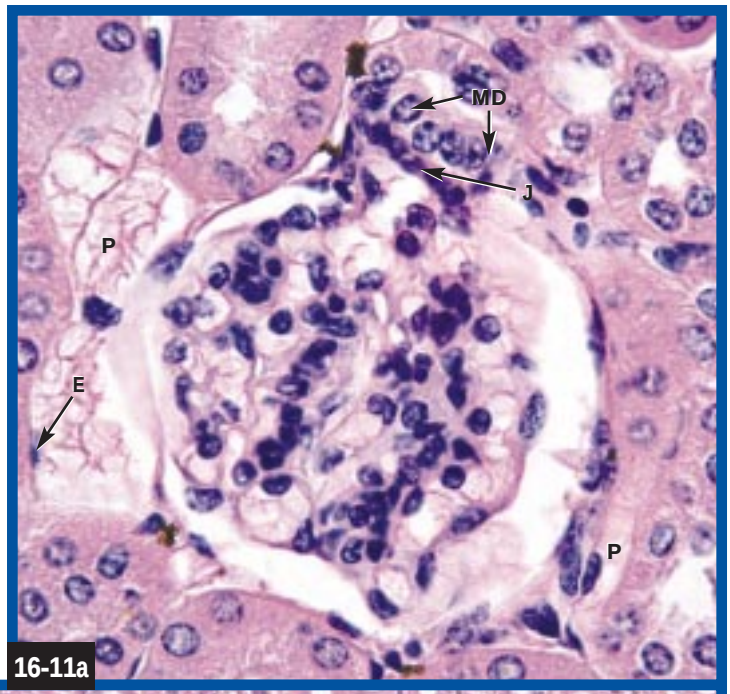
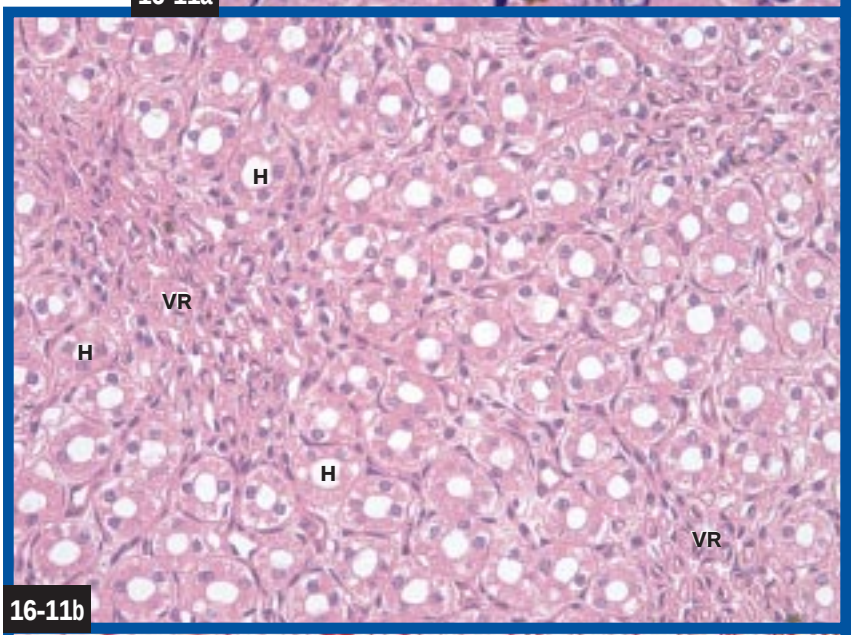
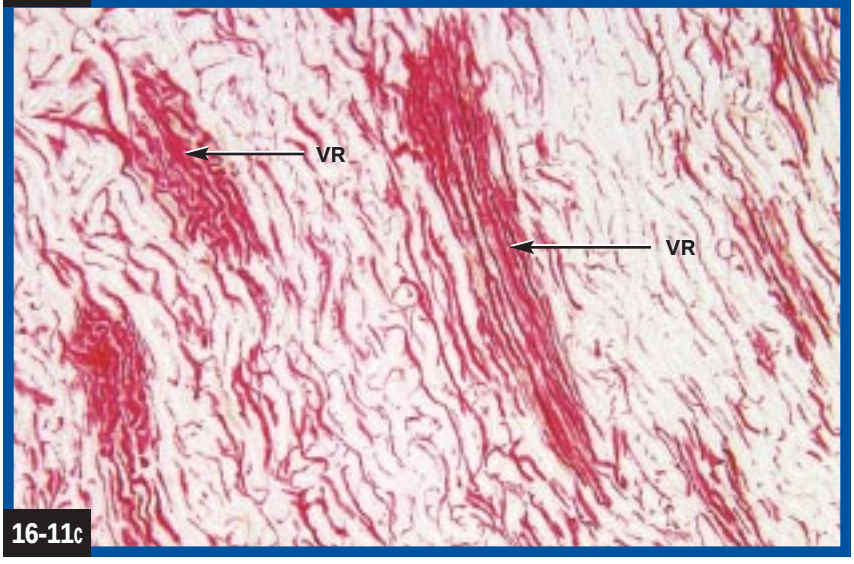
RENAL PAPILLA The medullary collecting tubules converge at the renal papilla to form papillary collecting tubules (ducts of Bellini). The papilla projects into the minor calyx (MC). *(X110)*







BLOOD VESSELS ASSOCIATED WITH THE NEPHRON (a) Peritubular capillaries (P) are found in the interstitium around proximal and distal convoluted tubules. Endothelial cell nuclei (E), and the macula densa (MD) and juxtaglomerular cells (J) of the JG apparatus are also seen in this specimen. (*X580*) (b) The vasa recta (VR) of the medulla near the cortex are often in bundles and are surrounded by thick segments of Henle's loop (H). (*X265*) (c) The vasa recta near the cortex are seen longitudinally in this injected specimen. *(X65)*

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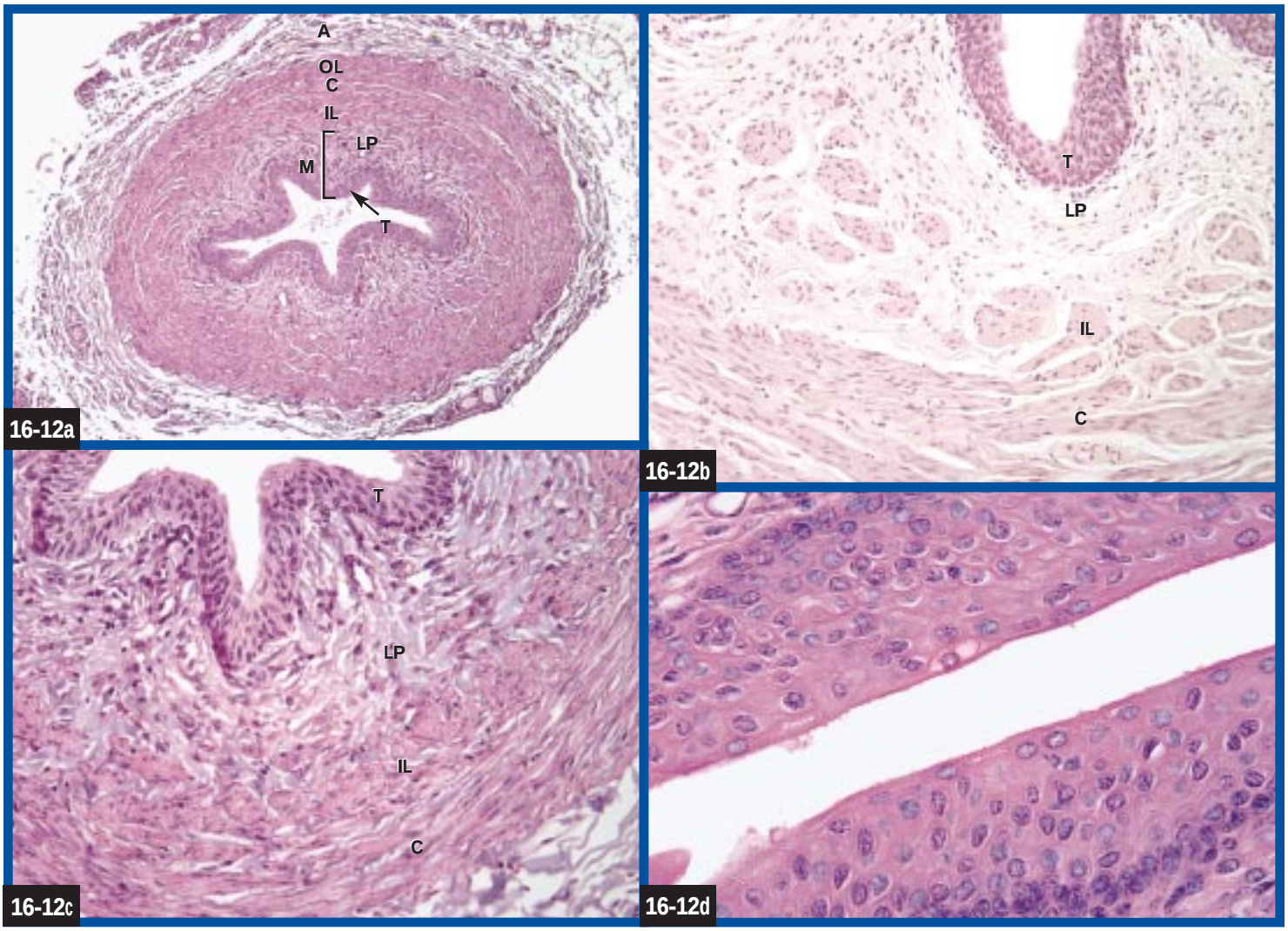
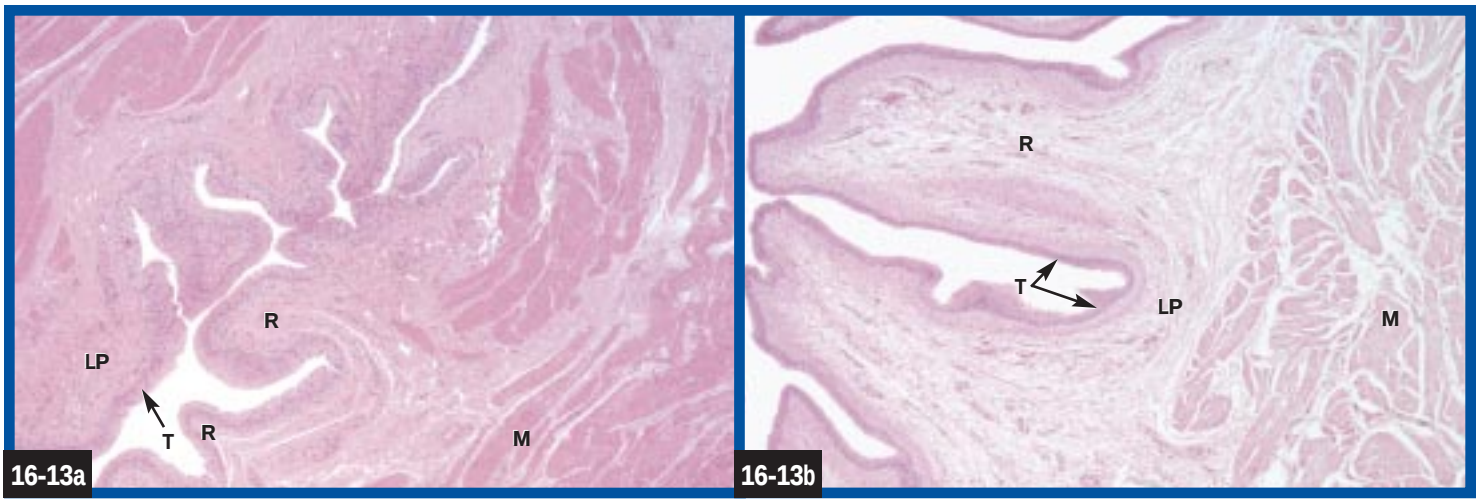


URETER The ureter wall consists of a mucosa (M) made of transitional epithelium (T) and a dense connective tissue lamina propria (LP). Inner longitudinal (IL) and outer circular (C) layers of smooth muscle comprise the muscularis. On the outer surface is a fibrous adventitia (A). (a) In the distal third of the ureter, an outermost longitudinal (OL) layer of smooth muscle is found. (*X50*) (b) This specimen was magnified X100. (c) This specimen was magnified X190. (d) The transitional epithelium lining the ureter is clearly seen in this longitudinal section. (*X320*)



URINARY BLADDER Transitional epithelium (T) and a lamina propria (LP) of superficial dense connective tissue and deeper loose connective tissue are in the mucosa of the urinary bladder. The mucosa has nonpermanent folds called rugae (R) that allow the bladder to accommodate filling with urine. The muscularis (M) has three indistinct layers of smooth muscle. On the outer surface is a fibrous adventitia or a serosa, but they are not shown in these micrographs. Both micrographs are X20.

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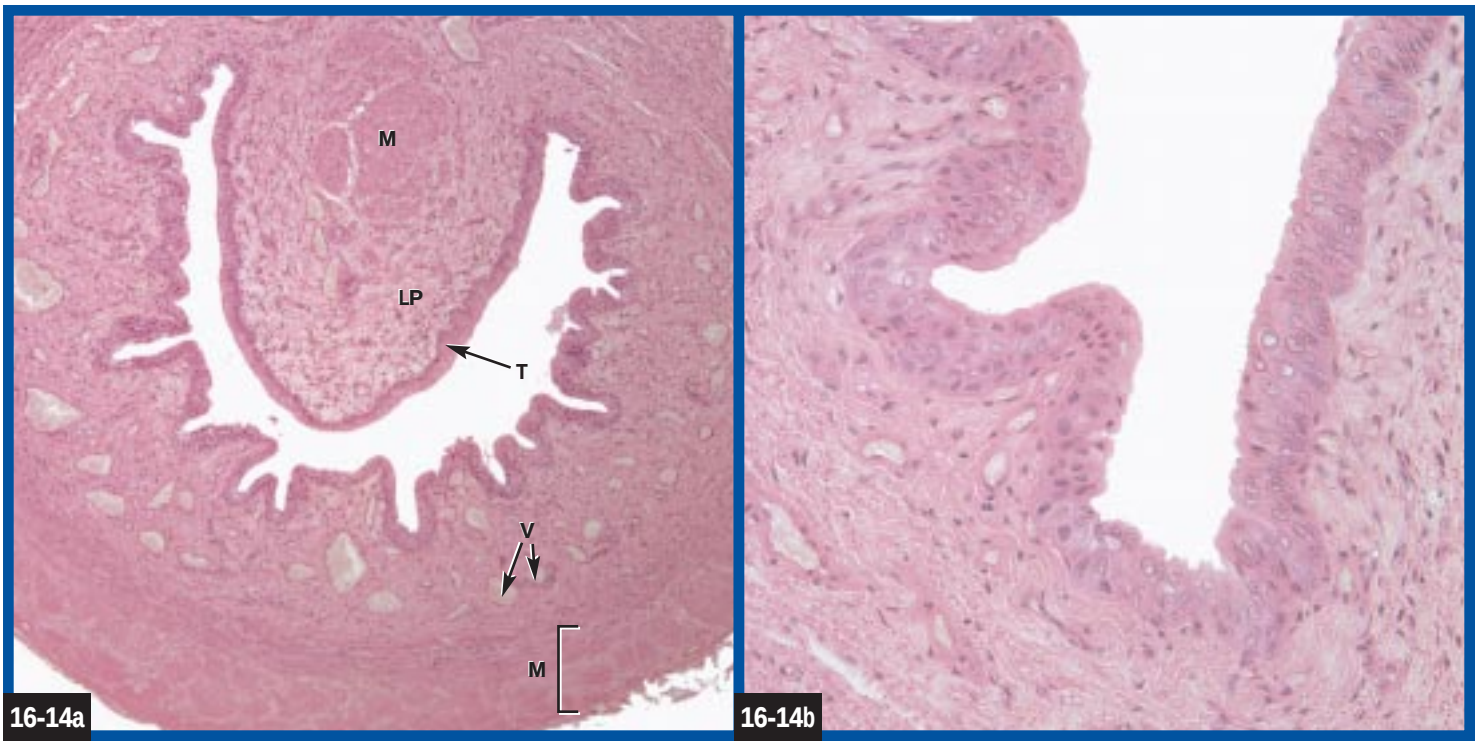
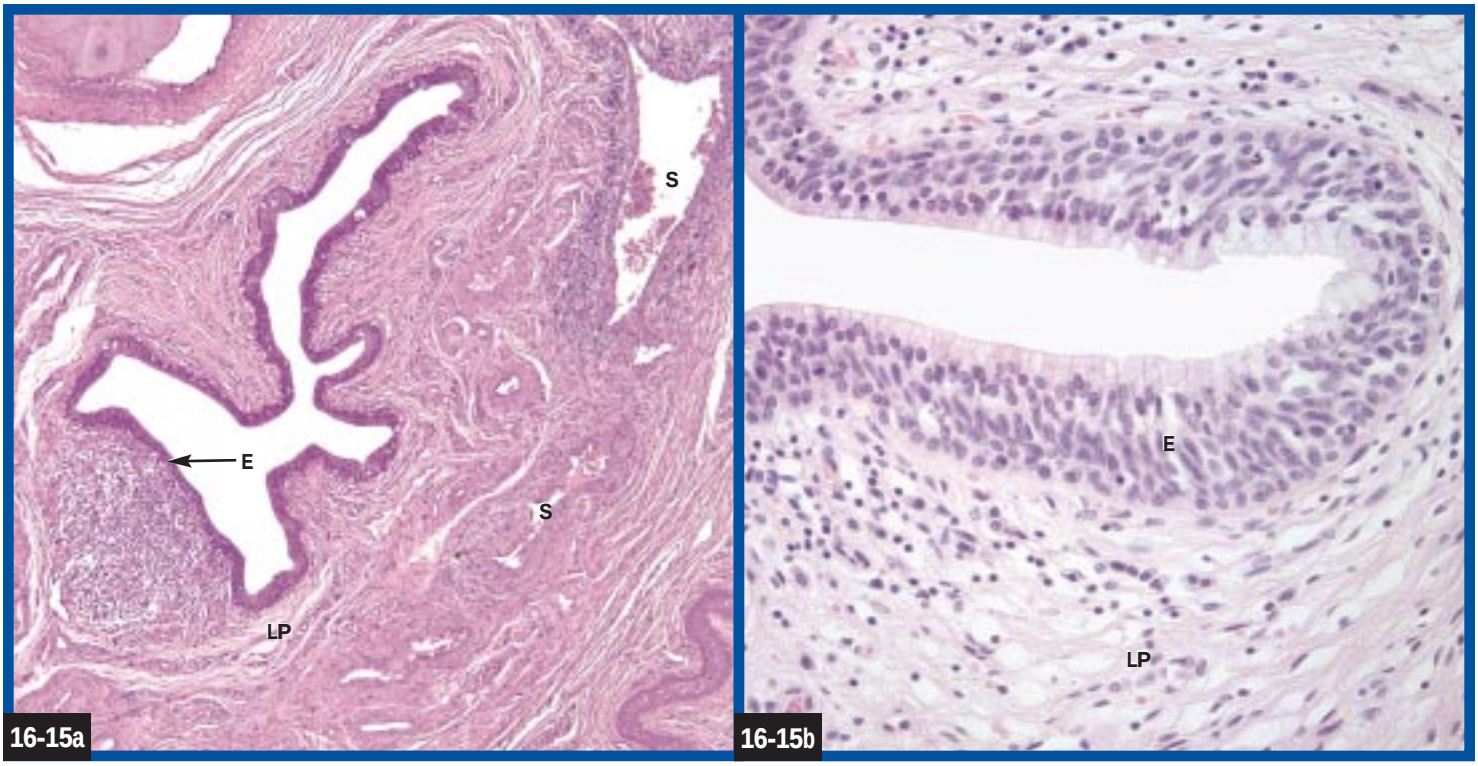


FEMALE URETHRA The female urethra is lined by a transitional epithelium (T) in the proximal segment and a nonkeratinized stratified squamous in the distal part. The mucosa is folded due to a highly elastic lamina propria (LP). Thin walled veins (V) form erectile tissue similar to the corpus spongiosum of the male. Inner longitudinal and outer circular smooth muscle layers comprise the muscularis (M). (a) In this panoramic view, the longitudinal mucosal folds and the venous sinuses are prominent. (*X100*) (b) The transitional epithelium indicates that this section is from the proximal urethra. (*X250*)



MALE URETHRA The male urethra differs in structure in its three segments. The epithelium of the prostatic urethra is transitional, but most of its length is stratified columnar (E) or PSCC. Shown in these micrographs is the longest portion, the spongy urethra. A fibroelastic lamina propria (LP) and blood sinusoids (S) of the corpus spongiosum surround it. (a) *X65* (b) *X250*

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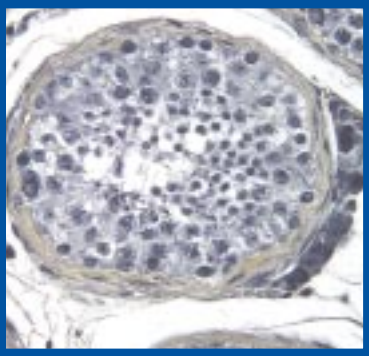
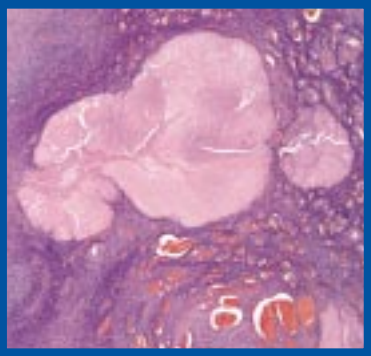
Reproductive Systems

CHAPTER 17

Introduction to the Reproductive Systems

The male and female reproductive systems are responsible for producing gametes (sex cells), a process known by the general term *gametogenesis*. Ova are the female gametes and are produced by *oogenesis*, whereas the male gamete, sperm, is produced by *spermatogenesis*. The organs responsible for gametogenesis are called gonads—ovaries in the female and testes in the male. In addition to gametogenesis, the gonads also produce sex hormones, which are necessary for reproduction as well as establishment of morphological sex in the male and secondary sex characteristics in both males and females. Lastly, the reproductive systems have organs of copulation—the penis of the male and the vagina of the female.

Male Reproductive System

The organs of the male reproductive system include the testes, epididymis, ductus deferens, ejaculatory duct, and urethra. Accessory glands include the prostate gland, seminal vesicles, and the bulbourethral glands.

Testes

The **testes** are the primary sex organs or **gonads** of the male. They develop in the abdominal cavity, then descend into the **scrotum** about the 28th week. In the adult, they are about 4 cm long and 2.5 cm in diameter.

Each testis is almost completely covered by a double layer of peritoneum called the **tunica vaginalis** obtained from the abdominal cavity during its descent into the scrotum. As with all serous membranes, there is an outer **parietal layer** and a **visceral layer** in contact the testicular surface. The space between is lubricated by serous fluid. Deep to the tunica vaginalis is a tough, thick fibrous covering called the **tunica albuginea** (Figure 17-1). Deep to the tunica albuginea is a layer of vascular loose connective tissue called the **tunica vasculosa.** Fibrous extensions of the tunica albuginea form **septa** and divide each testis into about 250 **lobules.** Each testicular lobule contains up to four **seminiferous tubules**, which are responsible for spermatogenesis. The seminiferous tubules empty into the **rete testis**, a network of tubules that lead to the **ductuli efferentes**, which carry sperm to the **epididymis** located on the posterior of the testis.

The interior of the testis is composed of seminiferous tubules and the testosterone producing **interstitial cells (of Leydig)** that occupy the vascular connective tissue (derived from the tunica vasculosa) between the seminferous tubules.

Each **seminiferous tubule** is up to 70 cm long and is composed of a thin connective tissue covering called the **tunica propria** and the relatively thick **germinal (seminiferous) epithelium** with its basal lamina. Contractile myoid cells are present in the tunica propria of some animals, but not humans. Several layers of spermatogenic cells in various stages of meiosis, which reduces the diploid chromosome number to the haploid number, and the taller Sertoli cells comprise the germinal epithelium.

Spermatogenic cells are the most abundant cells in the germinal epithelium (Figure 17-2). **Type A spermatogonial cells** are located near the basal lamina and undergo mitotic divisions to produce more type A cells as well as **type B spermatogonia.** The latter divide to produce **primary**

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spermatocytes, which migrate closer to the lumen. These are identifiable by their abundant cytoplasm and condensed chromatin in the nucleus. Primary spermatocytes undergo the first meiotic division to produce **secondary spermatocytes**, which are difficult to find because they immediately undergo **t**he second meiotic division and produce **spermatids** with dark staining nuclei. The haploid spermatids then undergo spermiogenesis, the conversion into a mature sperm cell, and are easily identified by their small and pointed nuclei and their position along the luminal surface.

Mature sperm cells (Figure 17-3) are composed of a head, midpiece, and tail. The **head** contains the haploid nucleus and is capped by the **acrosomal vesicle**. It is derived from Golgi apparatus and contains hydrolytic enzymes used in fertilization. The **midpiece** contains abundant mitochondria responsible for producing ATP necessary to operate the flagellum, which constitutes the **tail.**

Sertoli cells are columnar and have a basal nucleus with dispersed chromatin and a single nucleolus. They are responsible for nourishing the sperm cells during their development in the seminiferous tubule's wall. Spermatogenesis requires follicle stimulating hormone (FSH) from the anterior pituitary gland. Sertoli cells, which respond by producing and secreting an androgen binding protein into the lumen, are thought to be its target.

A round nucleus with dispersed chromatin and one or two nucleoli, and an eosinophilic cytoplasm with lipid vacuoles characterize the **interstitial cells** (Figure 17-4). They occupy the region between seminiferous tubules and are surrounded by numerous capillaries, into which they secrete the male sex hormone testosterone. It is necessary for embryonic development into a male, development of secondary sex characteristics, and normal sperm development. Interstitial cell activity is under the control of luteinizing hormone (LH) from the anterior pituitary.

Rete Testis, Ductulus Efferens, and Epididymis

The seminiferous tubules empty into a network of tubules called the **rete testis** (Figure 17-5). These are lined with a simple cuboidal epithelium whose cells have microvilli and a single cilium. Contraction of surrounding **myoid cells** and ciliary action move sperm along the tubule.

Fifteen to twenty **ductuli efferentes** receive sperm from the rete testis and deliver them to the epididymis where they mature and become motile. The efferent ductules are lined with simple ciliated columnar or simple nonciliated cuboidal epithelium. A thin smooth muscle layer is also present.

An **epididymis** (Figure 17-6) is found on the posterior of each testis. It consists of a **head** (superior), **body** and **tail** (inferior) and is the site of sperm storage and final maturation, which includes developing motility. It is lined with a pseudostratified epithelium that is thicker at the head than at the tail. Long microvilli, called **stereocilia** (a misnomer), project from the tallest cells and are involved in reabsorption of fluid. Smooth muscle increases from a single circular layer at the head to three layers in the tail resembling what is seen in the ductus deferens.

Ductus Deferens and Ejaculatory Duct

The **ductus (vas) deferens** (Figure 17-7) is a muscular tube that carries sperm from the epididymis to the urethra. Its terminal portion, the **ampulla,** is dilated and joins with the seminal vesicle to form the **ejaculatory duct.** The **mucosa** is folded longitudinally and is lined with a pseudostratified columnar epithelium resting on a thin **lamina propria**. The thick **muscularis** is composed of an **inner longitudinal**, a **middle circular**, and an **outer longitudinal** layer of smooth muscle. These produce peristaltic contractions during ejaculation.

Urethra

The **male urethra** (Figures 16-15 and 17-10) is between 15 and 20 cm long. Three segments are identifiable based on location. These are the prostatic urethra, membranous urethra, and spongy (penile) urethra. The **prostatic urethra** passes through the prostate gland and is lined with transitional epithelium. The microscopic prostatic ducts and the two ejaculatory ducts empty into it. The **membranous urethra**, lined with stratified columnar epithelium, passes through the urogenital diaphragm. This segment is the site of the external urinary sphincter. The **spongy (penile) urethra** is found within the **corpus spongiosum** of the penis. It is lined with stratified columnar or PSCC epithelium with stratified squamous at the **external urethral orifice**.

Seminal Vesicle

The **seminal vesicles** (Figure 17-8) produce a secretion rich in fructose, prostaglandins, and other materials. The **mucosa** is highly folded and is lined with a **pseudostratified epithelium**. The secretory cells are tall and have a foamy appearance due to the lipid contents. A **muscularis** consisting of an inner circular layer and an outer longitudinal layer of smooth muscle creates peristaltic contractions during ejaculation and forces the secretion into the ejaculatory duct.

Prostate Gland

The **prostate gland** (Figure 17-9) is about 4 cm long and 3 cm wide and is found inferior to the urinary bladder. It surrounds the proximal (prostatic) urethra and also surrounds the ejaculatory ducts. Its secretion is rich in many chemicals, including citric acid, lipids, and proteolytic enzymes.

A vascular dense irregular connective tissue **capsule** containing smooth muscle cells surrounds the prostate and penetrates into the gland as the **stroma**. Up to 50 tubuloalveolar glands are arranged into concentric layers around the urethra. The **mucosal glands** form the layer next to the

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urethra. These are surrounded by the **submucosal glands** and the **main glands,** which comprise the thickest layer. A simple to pseudostratified columnar epithelium lines them. **Pancreatic concretions (corpora amylacea)** are often found inside the glands. They are made of glycoprotein and are of unknown function, but they do increase with age.

Penis

The **penis** is a cylindrical organ that functions in urine elimination and as the male copulatory organ. It is covered with skin, which is hairless at the distal end, but has coarse hairs proximally. A loose hypodermis is also present.

Internally, three cylindrical bodies of erectile tissue run its length (Figure 17-10). These are the two dorsal **corpora cavernosa** and the ventral **corpus spongiosum**, which surrounds the **spongy urethra**. A fibrous connective tissue layer called the **tunica albuginea** surrounds each cavernous body. The erectile tissue is composed of vascular spaces lined with endothelium and separated by connective tissue trabeculae. These spaces fill with blood during erection.

Semen

Semen contains only about 5% sperm cells by volume. The seminal vesicles (70%), prostate gland (25%), and bulbourethral glands (minimal) contribute the remainder of seminal fluid.

Female Reproductive System

Female reproductive organs include the ovaries, uterus and fallopian tubes, vagina, and breasts with mammary glands. In addition, the placenta and umbilical cord are organs of pregnancy.

Ovary

Ovaries are the female **gonads** (Figure 17-11). Like the testes, the ovaries have a gametogenic and an endocrine function. A simple cuboidal epithelium called **germinal epithelium** and derived from peritoneum covers each ovary. Deep to it is the thin **tunica albuginea**, made of dense irregular connective tissue. The bulk of the ovary is divided into a cellular **cortex** and a loose connective tissue **medulla**, although the boundary between them is not sharp.

Within the ovarian cortex (Figure 17-12) are developing **ovarian follicles** surrounded by a connective tissue **stroma.** The embryonic ovarian cortex is populated by **oogonial cells** from the yolk sac. Of the 5 to 7 million original oogonial cells, only about 1 million become surrounded by follicle cells to form **primordial follicles** and survive to the female child's birth. The cells derived from oogonia are called **primary oocytes** and they are suspended in prophase of meiosis I until they continue development just prior to ovulation. Only about 400,000 primordial follicles survive to the beginning of puberty. Of these, only about 450 reach full maturity over a woman's reproductive years at a rate of one per month.

Beginning with puberty and approximately every 28 days thereafter until menopause, and under the influence of Follicle Stimulating Hormone (FSH) from the anterior pituitary, primordial follicles continue their development. At this stage of development, the primordial follicles consist of a single layer of flat cells surrounding the primary oocyte. The primary oocyte has a large, eccentric nucleus with one nucleolus and is approximately 25 µm in diameter. Development continues as the primary oocyte enlarges to about 100 µm and the follicle cells, now called **granulosa cells** (that form the **zona granulosa**), become stratified to form a **multilaminar primary follicle**. The **zona pellucida**, an amorphous glycoprotein layer, forms between the primary oocyte and the granulosa cells. In addition, the stroma near the follicle forms an inner vascular and cellular layer called the **theca interna**, and an outer fibrous layer called the **theca externa.** The theca interna and granulosa cells produce the hormone **estrogen.**

Development of a primary follicle into a **secondary follicle** involves continued proliferation of the granulosa cells and the formation of small intercellular spaces that coalesce to form the **antrum**. **Follicular fluid (liquor folliculi)** accumulates in the antrum. Some granulosa cells remain around the oocyte and form the **cumulus oophorus**. Further development results in the layer of cells next to the zona pellucida retracting from the oocyte but remaining attached via thin cytoplasmic threads. This single layer of cells is called the **corona radiata**.

Of the many secondary follicles that form each month, only a few continue development into a mature **Graafian follicle,** which attains a size of 2.5 cm and bulges from the ovary's surface. The primary oocyte and the corona radiata detach and float free in the follicular fluid until ovulation. The primary oocyte completes the first meiotic division and forms a **secondary oocyte** and the **first polar body**. Most of the cytoplasm ends up in the secondary oocyte; the polar body serves its purpose by carrying the second haploid nucleus produced by meiosis I. Then, the secondary oocyte begins the second meiotic division.

Ovulation is a complex process, but basically is associated with a spike of Luteinizing Hormone (LH) from the anterior pituitary gland, which leads to two events. These are an increased internal pressure due to follicular fluid accumulation, and the weakening and rupture of the follicle's granulosa cells near the ovarian surface. The secondary oocyte enters the **infundibulum** of the **fallopian tubes** (see next page) and begins its journey toward the uterus and, perhaps fertilization. If fertilization does not occur within about 24 hours after ovulation, the secondary oocyte is phagocytosed.

Meanwhile, under the influence of luteinizing hormone (LH) the granulosa cells remaining in the ovary form a **corpus**

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hemorrhagicum, which develops into a **corpus luteum** (Figure 17-13). The majority of corpus luteum cells is derived from the granulosa cells. These **granulosa-lutein cells** are large and pale staining, and secrete progesterone and estrogens. Cells derived from the theca interna cells are at the periphery and are smaller, fewer in number, and darker staining than the granulosa lutein cells. They are called **theca-lutein cells** and also produce progesterone and estrogens. Failing fertilization, this **corpus luteum of menstruation** dies and becomes replaced with fibroblasts to form the **corpus albicans** (Figure 17-14).

If fertilization does occur, the corpus luteum continues enlarging to a size of 5 cm and forms a **corpus luteum of pregnancy** (Figure 17-15), which supplies estrogens and progesterone necessary to maintain the pregnancy. The placenta assumes this function after about 3 months, but the corpus luteum continues to contribute for several months into the pregnancy.

The **ovarian medulla** (Figure 17-11a) consists of a loose, fibrous connective tissue with large blood vessels, lymphatics, and nerves. The main cells are fibroblasts and the epithelioid **hilus cells** that produce androgens.

Fallopian Tube

The **fallopian (uterine) tubes** are lateral extensions from the superior portion of the uterus. There are four segments to each. These are the infundibulum, ampulla, isthmus, and intramural region. The **infundibulum** is the funnel-shaped, open end that receives the ovulated secondary oocyte from the ovary. It has fingerlike projections called **fimbriae** extending from its margin. The **ampulla** is the longest portion of the fallopian tubes and is the usual site of fertilization. Where the ampulla becomes more constricted, it forms the **isthmus**, which leads to the **intramural region** within the uterine wall.

There are three layers in the fallopian tubes (Figure 7-16). These are the mucosa, muscularis, and serosa. The **mucosa** forms longitudinal folds, which are branched in the ampulla, and is lined with a simple columnar epithelium. **Ciliated cells** sweep the oocyte and fluid formed by **nonciliated secretory (peg) cells** toward the uterus. The secretion also nourishes the sperm and assists in their final maturation. Deep to the epithelium is an unremarkable **lamina propria** made of a loose connective tissue. Movement of the oocyte is also assisted by peristaltic waves produced by an **inner circular** and an **outer longitudinal layer of smooth muscle**. The whole fallopian tube is covered with peritoneum, which forms the **serosa**.

Uterus

The **uterus** is a pear-shaped organ, 7 cm by 4 cm, located in the pelvic cavity. There are three regions of the uterus. These are the body, fundus, and cervix. The **uterine body** is the major portion of the organ. The fallopian tubes enter the superior portion of the body. The **fundus** is located superior to the entry of the fallopian tubes. The **cervix** is the cylindrical portion that projects into the vagina.

The uterine wall is composed of three major layers (Figure 17-17). These are the endometrium, myometrium, and perimetrium. The **endometrium** is the uterine mucosa and is the site of **blastocyst** (the multicellular derivative of the fertilized ovum after about one week of development) implantation during pregnancy. It is lined with a simple columnar epithelium overlying a vascular **stroma**. Glycogen-secreting simple tubular **uterine glands** are the most distinctive feature of the uterine mucosa. During the proliferative (follicular) phase of the menstrual cycle, these glands elongate and become coiled under the influence of ovarian estrogen. Coincident with this, the stroma gets thicker and more vascular. Glycogen secretion and the vascularity of the stroma both serve to support the implanted blastocyst until the placenta forms. The secretory (luteal) phase begins after ovulation. During this phase the endometrium is maintained by luteinizing hormone from the corpus luteum. If no fertilization and implantation occur, progesterone levels decrease as a result of the corpus luteum dying and the endometrium is shed during menstruation.

The cyclic growth, death and repair of the endometrium have resulted in the recognition of three layers in it (Figure 17-18). The **stratum basalis** is next to the myometrium and is relatively unchanged during the cycle. It serves as the source of new endometrium after menstruation. The thickest layer, characterized by a spongy looking stroma is the **stratum spongiosum**. On the surface is the thin **stratum compactum**, characterized by a denser stroma. Together, the stratum spongiosum and compactum undergo the most change during the menstrual cycle and are collectively referred to as the **stratum functionalis**.

Straight arteries and **spiral arteries** supply the endometrium. The former provide blood to the stratum basalis, whereas the latter supply the stratum functionalis. The spiral arteries constrict in the absence of progesterone, which makes the stratum functionalis ischemic, resulting in its death.

The **myometrium** (Figure 17-19) is composed of smooth muscle in three poorly defined layers. There are inner and outer longitudinal layers with a thick circular layer between. The outer surface of the fundus and posterior body is covered with a **serosa (parietal peritoneum)**. The remainder is covered with a fibrous **adventitia**.

The **cervix** (Figure 17-20) is divided into an **endocervical canal** and an **ectocervix**, which protrudes into the vagina. The endometrium of the endocervical canal is lined by a mucous secreting simple columnar epithelium, which also lines depressions called **endocervical glands.** The ectocervix resembles the vagina in that it is lined with a stratified squamous epithelium. The myometrium is mostly

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replaced with elastic connective tissue as an adaptation to the stretching necessary during childbirth. Lymphocytes may be seen in this layer near the surface.

Vagina

The **vagina** (Figure 17-21) is the female copulatory organ and serves as the birth canal. It is about 9 cm long and is lined with a **mucosa** composed of **nonkeratinized stratified squamous epithelium** and a dense, elastic **lamina propria.** The mucosa folds when relaxed and the lumen is closed. There are no vaginal glands; cervical mucus is primarily responsible for its lubrication. Deep to the mucosa is a **muscularis** composed of an **inner circular** and an **outer longitudinal layer** of smooth muscle, though they are not well-defined and the fibers mix. Deep to the muscularis is a fibrous **adventitia**, which blends in with the adventitial layers of the urinary bladder and rectum.

Breast

The **breasts** contain **mammary glands** and are responsible for producing milk (Figure 17-22). Mammary glands are present in both sexes, but under the influence of estrogen, progesterone and prolactin (from the anterior pituitary gland) in the female, the glands develop further. The 15 to 25 **lobes** in each breast are made of independent **compound tubuloacinar glands**. A **lactiferous duct** drains the gland to a **lactiferous sinus,** which leads to the nipple. The glands are surrounded by **adipose tissue** and are separated by fibrous **septa**. The skin covering the nipple has sebaceous glands not associated with hair follicles.

During pregnancy, the mammary glands branch and grow into **alveoli**, *composed of a* **simple columnar epithelium** *and surrounded by* **myoepithelial cells**. *Initially they produce a viscous, protein-rich substance called colostrum; within a few days after the child is born, they produce true milk.*

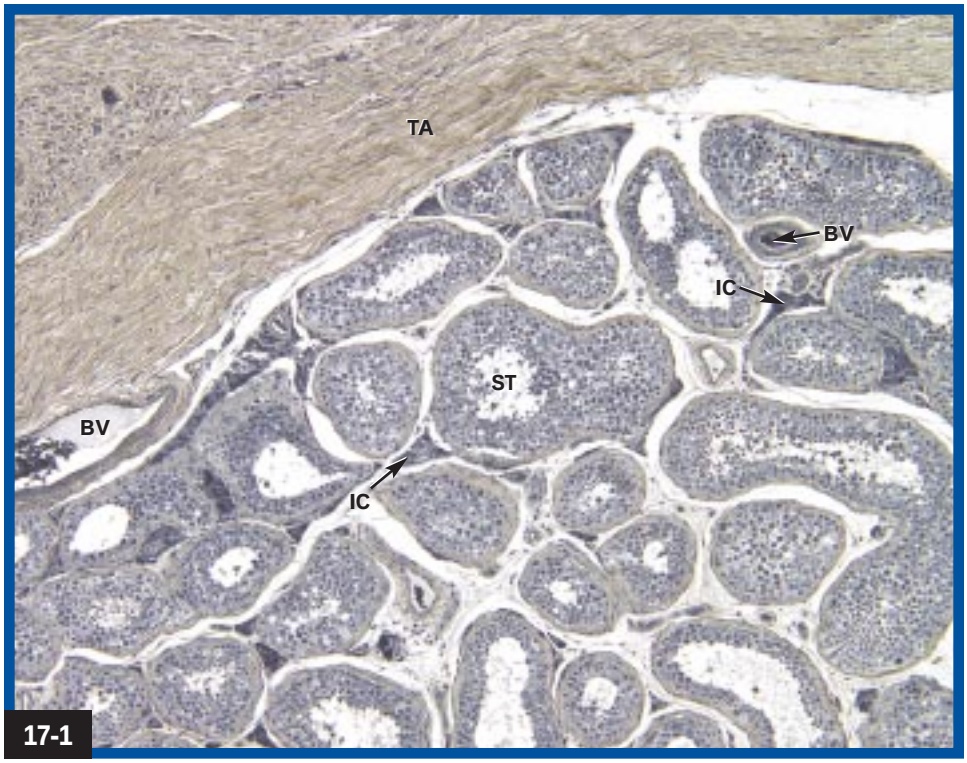
Placenta

The **placenta** (Figure 17-23) is a complex organ that connects the embryo/fetus with the mother's uterus. It is constructed from embryonic and maternal tissues. The fully formed placenta serves as the fetus' kidneys, lungs, and intestines. That is, it absorbs oxygen and nutrients from maternal blood, and transfers metabolic wastes into it. Under normal circumstances, there is no mixing of maternal and fetal blood—no blood cells cross the **placental barrier** (see next column).

The placenta is attached to the endometrium by a structure known as the **decidua basalis**, derived from the endometrial stratum functionalis. Beginning with the third month, **chorionic villi** anchor the developing embryo to the decidua basalis. In the mature placenta, the villi are branched and are not attached. Thus, **free villi** outnumber **anchoring villi**. Both types are covered with a cellular layer composed of **syncytial trophoblasts**, whose nuclei are seen to form clusters called **syncytial knots.** The core of each villus contains **fetal capillaries** (and sometimes larger vessels), and embryonic **mesoderm**. Open spaces in the decidua called **lacunae** or **intervillous spaces** surround the villi and contain maternal blood. Thus, the villi are bathed in maternal blood, but the syncytial trophoblasts and connective tissue form the placental barrier and prevent mixing with fetal blood**.**

Umbilical Cord

The **umbilical cord** (Figure 17-24) is derived from the early connecting stalk that attaches the embryo to the trophoblast layer. When fully formed, it is covered by **amniotic membrane** and is filled with a ground substance called **Wharton's jelly**, which contains mesenchymal cells. The two **umbilical arteries**, which carry oxygen-poor blood to the chorionic villi, and the single **umbilical vein**, which brings oxygen-rich blood to the fetus, are also present.



TESTIS In this micrograph, the fibrous tunica albuginea (TA) of the testis and a portion of a lobule are visible. Also seen are seminiferous tubules (ST), intestinal cells (IC), and a couple of blood vessels (BV). *(X65)*

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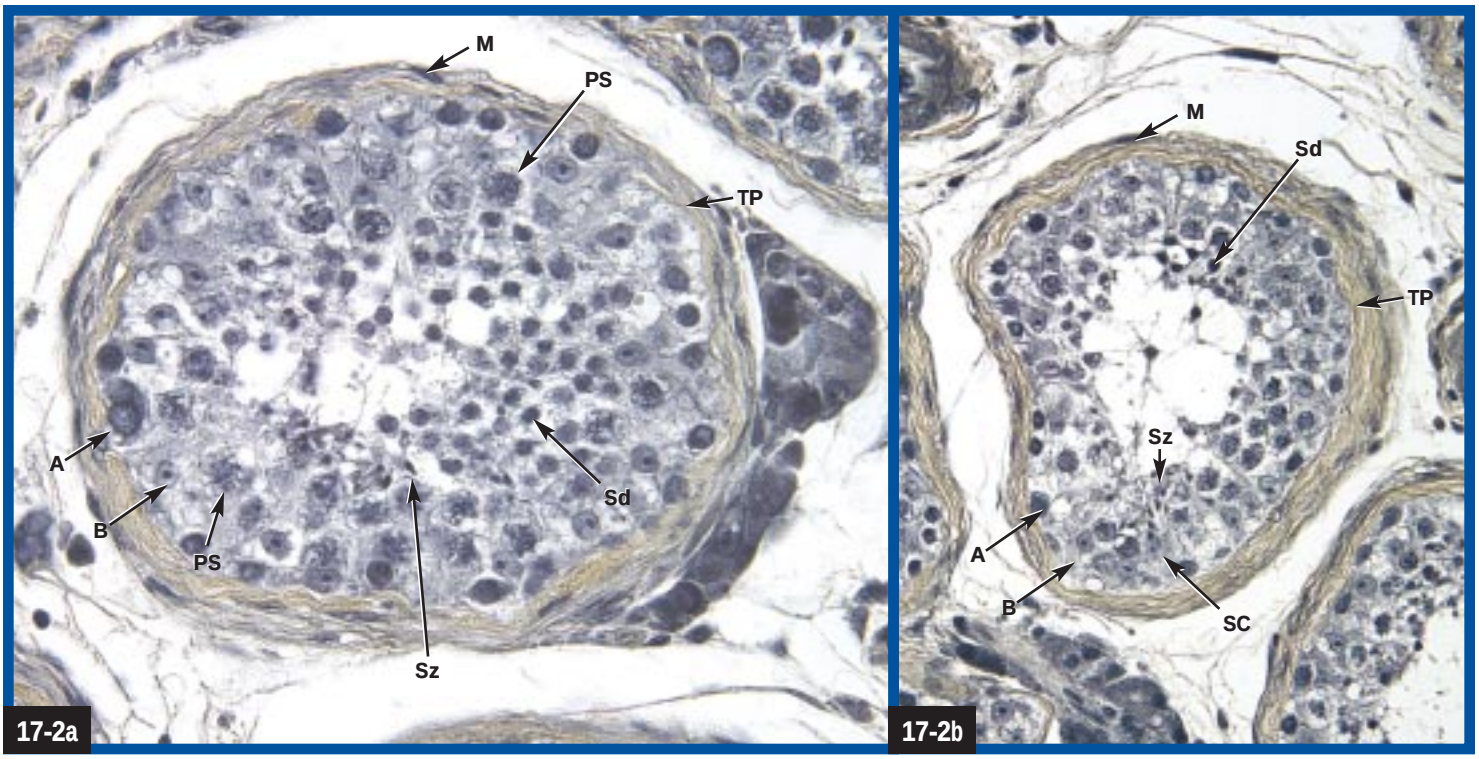
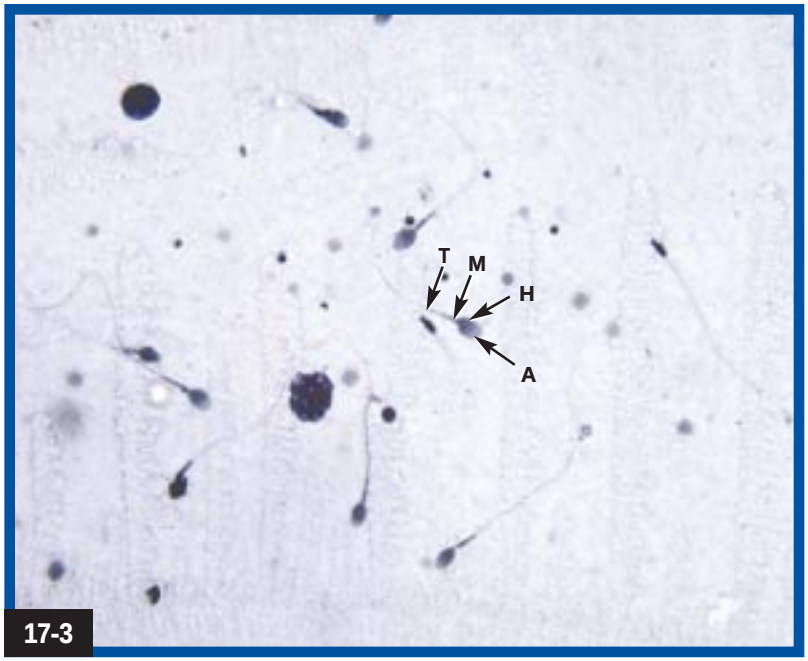


SEMINIFEROUS TUBULES Stages of spermatogenesis and spermiogenesis are visible in these micrographs. Type A spermatogonia (A) are identifiable by their basal position in the tubule and a round nucleus with condensed chromatin and a nuclear vacuole. Type B spermatogonia (B) lack the vacuole and have dispersed chromatin with a prominent central nucleolus. Primary spermatocytes (PS) are located closer to the lumen. They are large cells with clumped chromatin. Secondary spermatocytes divide quickly after their production and are rarely seen in histological preparations. Spermatids (Sd) are small cells with round, dark nuclei. Spermatozoa (Sz) have pointed nuclei. Sertoli cells (SC) are located near the base of the tubule and are characterized by an ovoid nucleus with a prominent nucleolus. In addition to cells of the spermatogenic series, note the fibromuscular tunica propria (TP) surrounding this tubule. Several myoid cells (M) are visible. Micrographs (a) and (b) were magnified X400 and X265, respectively.



SPERM CELLS The head (H), midpiece (M), and tail (T) are visible in these sperm cells. Also visible in some is the acrosome (A). *(X660)*

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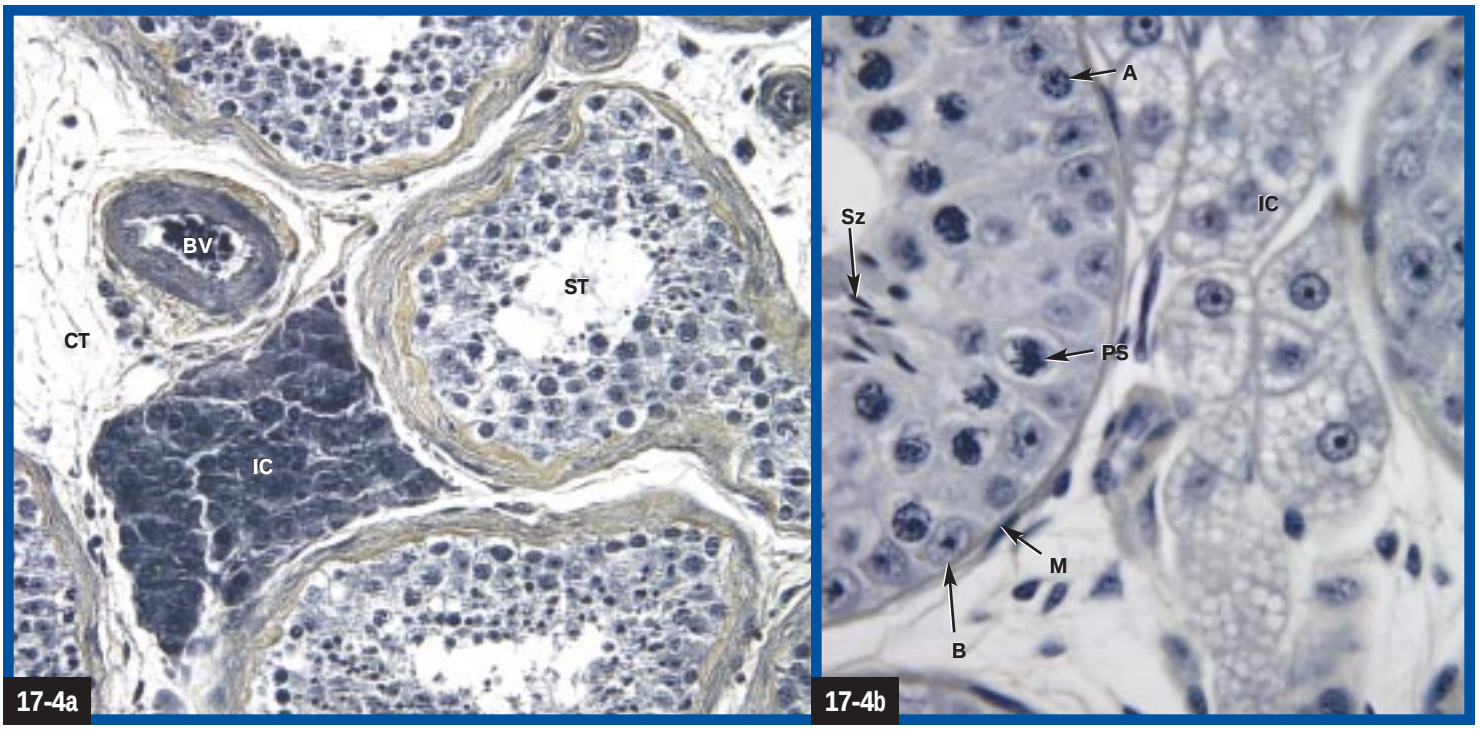
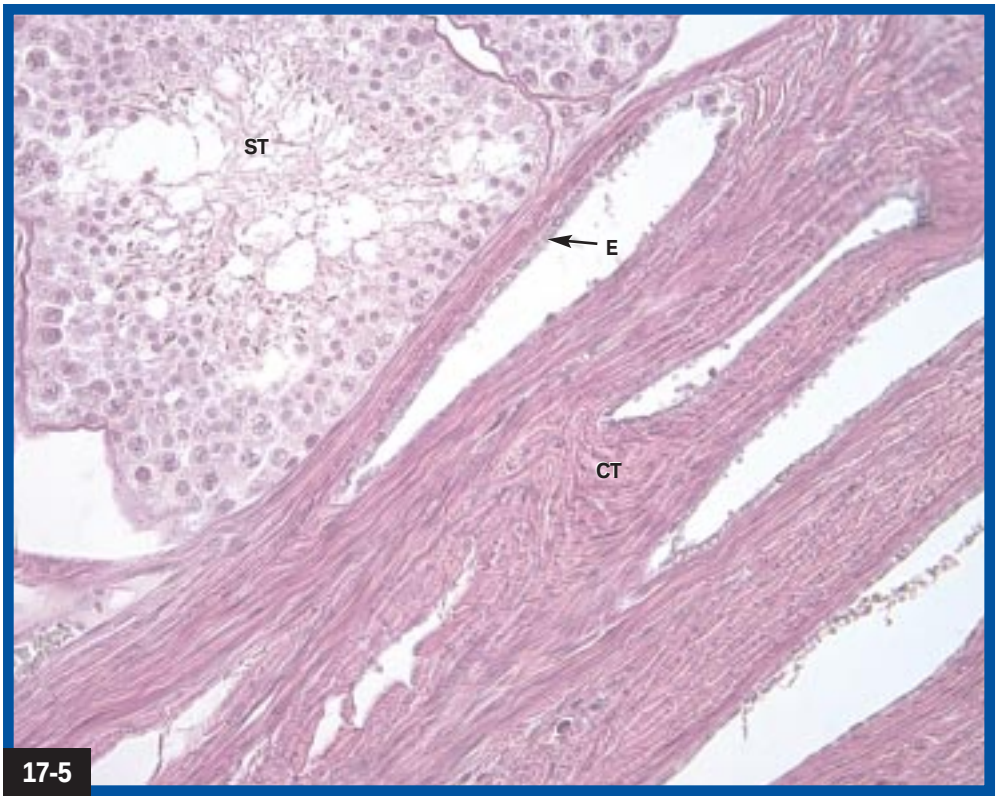


INTERSTITIAL CELLS OF LEYDIG Interstitial cells (IC) are found in the vascular connective tissue (CT) located between seminiferous tubules (ST) and constitute the main endocrine portion of the testis. (a) The interstitial cells are dark in this micrograph, but the nuclei with prominent nucleolus are discernible. Note the blood vessels (BV) in the connective tissue. *(X230)* (b) In this micrograph, the interstitial cells and their lipid vacuoles, characteristic of steroid secreting cells, are easily seen. Note also the spermatogenic cells and myoid cells of the seminiferous tubule. Symbols used are the same as in Figure 17-2. *(X580)*



RETE TESTIS Seminiferous tubules empty into the rete testis, a network of tubules lined with simple cuboidal epithelium (E) having microvilli. Each cell also has a single cilium. A vascular connective tissue (CT) and myoid cells surround the tubules. A seminiferous tubule (ST) is also seen. *(X265)*

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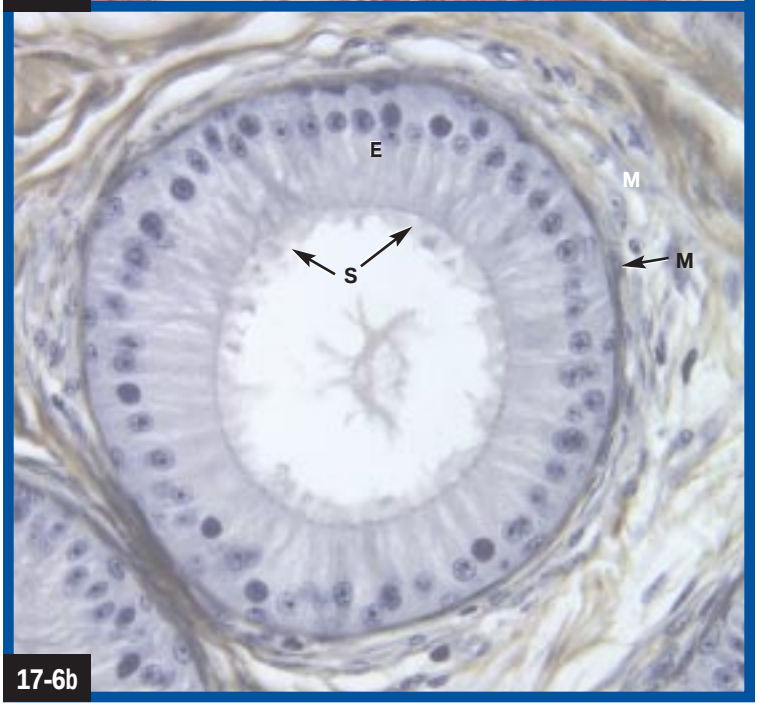
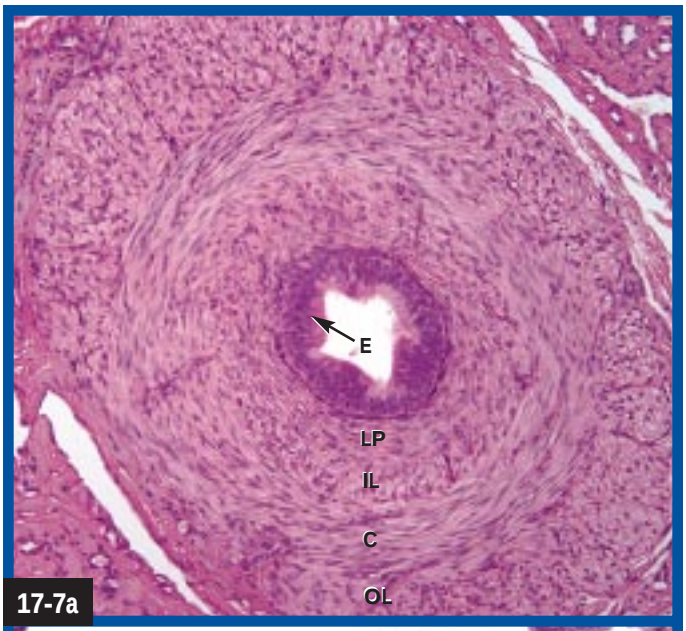
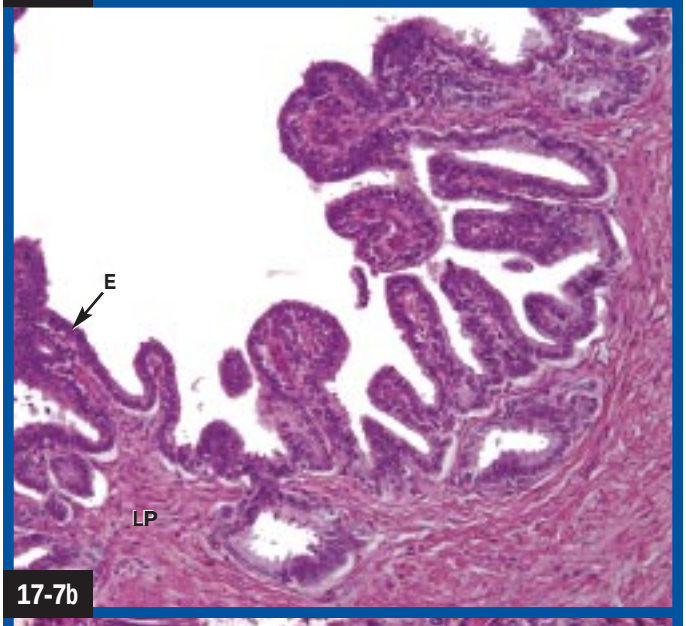
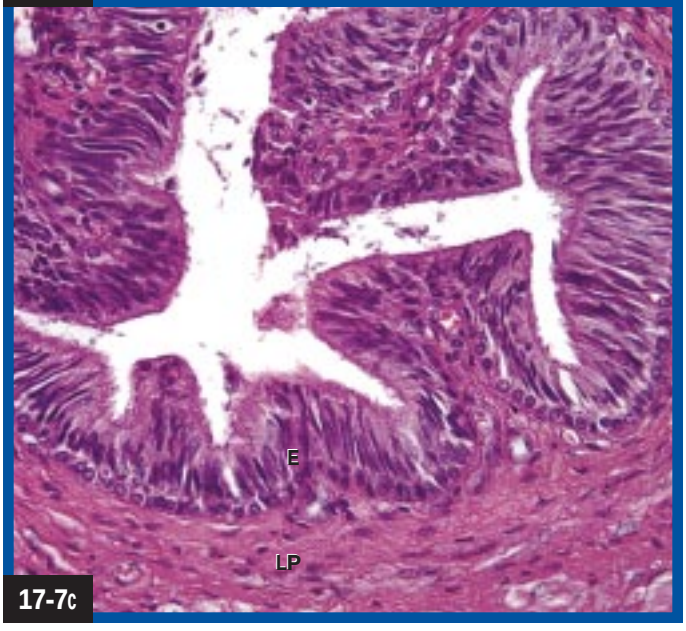


EPIDIDYMIS Pseudostratified epithelium (E) lines the ducts of the epididymis. The tallest cells have long microvilli (stereocilia) (S), which aid in fluid absorption. The amount of smooth muscle (M) in the ducts' walls increases toward the ductus deferens. (a) *X130* (b) *X380*







DUCTUS DEFERENS The longitudinally folded mucosa of the ductus (vas) deferens consists of a pseudostratified epithelium (E) and connective tissue lamina propria (LP). The very muscular wall is composed of inner (IL) and outer longitudinal (OL) smooth muscle layers, with a circular (C) layer between. (a) *X110* (b) *X110* (c) *X215*

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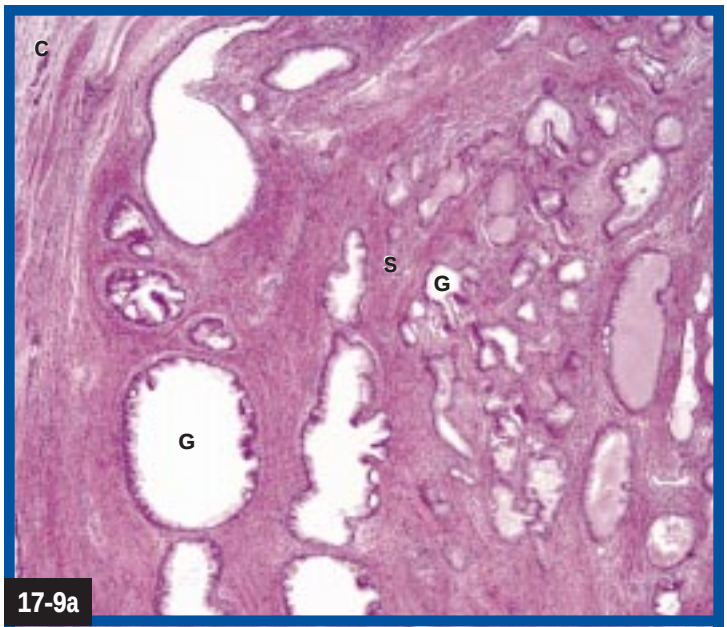
17-8a

17-8b

SEMINAL VESICLE Each seminal vesicle joins a ductus deferens and empties its fructose-rich secretion into it. The mucosa is lined with a pseudostratified epithelium (E). These cells have lipid droplets in them, which often results in a foamy appearance. Lipofuchsin granules are also sometimes seen. The muscularis consists of an inner circular (C) and an outer longitudinal (L) layer. (a) *X25* (b) *X110*



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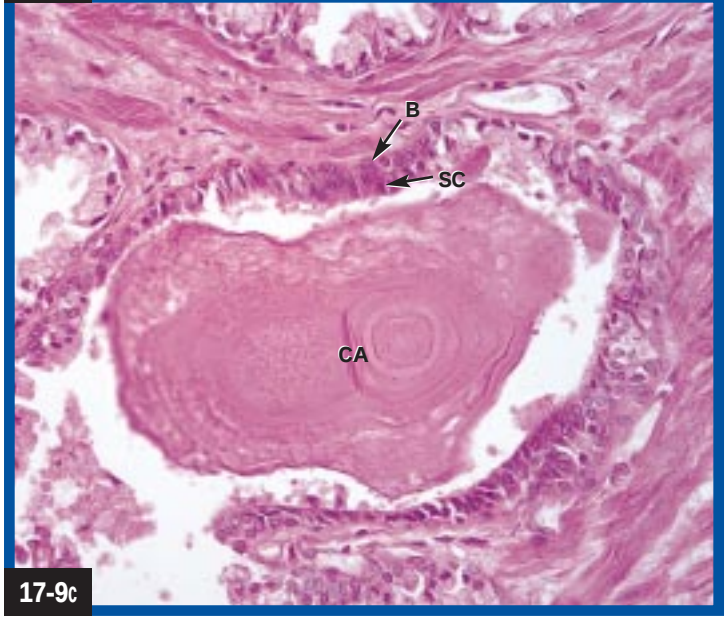

17-9c

PROSTATE GLAND Shown here are three micrographs of the prostate gland. Branched tubulo-acinar glands (G) predominate and are lined with basal cells (B) and surface secretory cells (SC). A fibromuscular stroma (S) fills the space between glands. Corpora amylacea (CA), made of glycoprotein, are found in the glands and increase with age. (a) A portion of the capsule (C) is visible in this micrograph. *(X25)* (b) The branching is apparent in this gland. *(X120)* (c) Corpora amylacea become calcified with age to form prostatic concretions. *(X240)*

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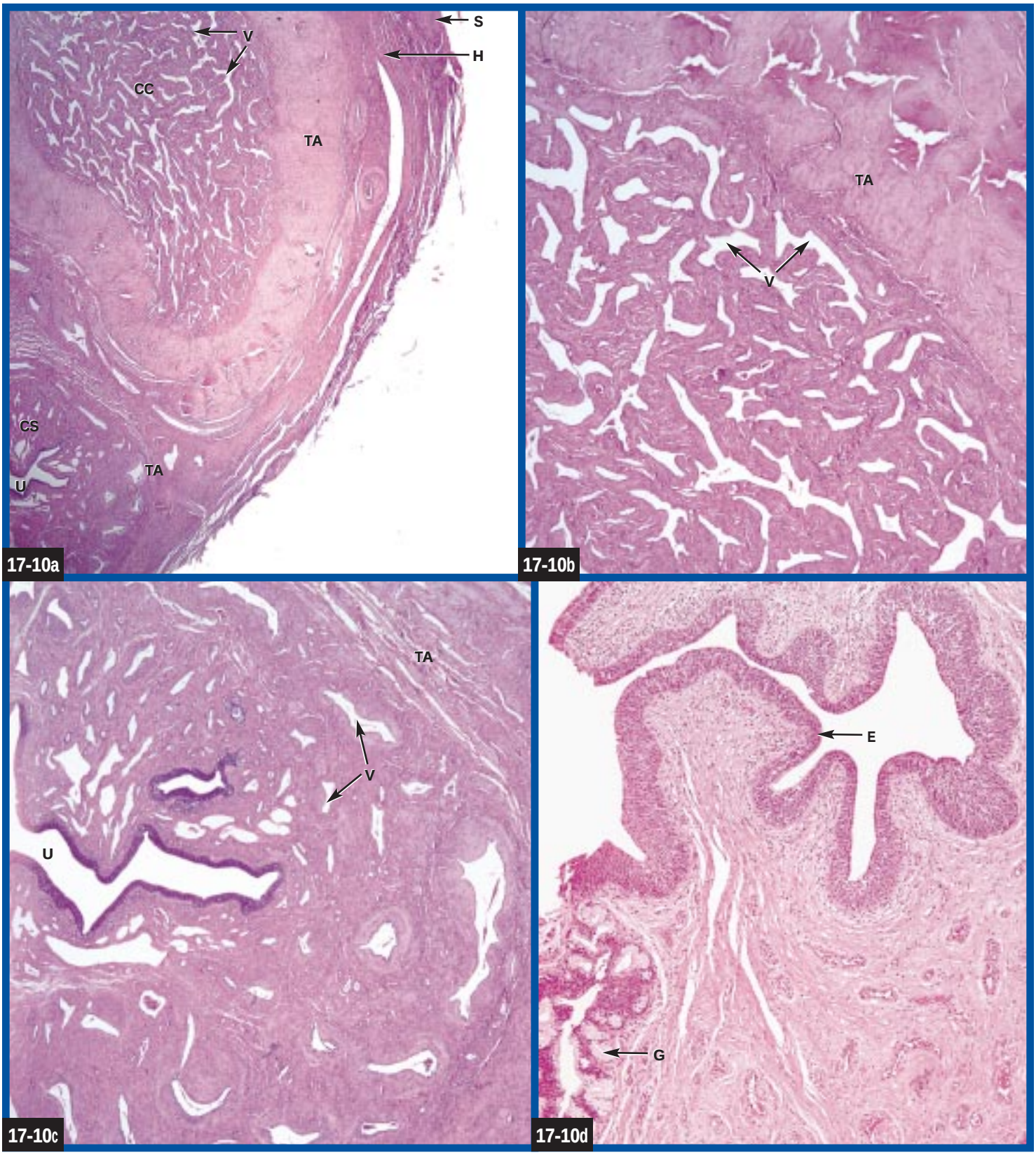

PENIS Externally, the penis is covered with skin (S) and a loose hypodermis (H). Internally, three cylinders of erectile tissue are present. These are the two dorsal corpora cavernosa (CC) and the ventral corpus spongiosum (CS) around the urethra (U). Each is surrounded by a fibrous connective tissue layer called the tunica albuginea (TA) and contains endothelium lined venous sinuses (V). (a) This micrograph is a transverse section of half a penis. *(X7)* (b) The venous sinuses and the tunica albuginea of the corpus cavernosum are seen in this micrograph. *(X25)* (c) The urethra is visible in the center of the corpus spongiosum. Note the tunica albuginea is thinner than in the corpora cavernosa. *(X25)* (d) The spongy (penile) urethra is lined with a stratified or pseudostratified columnar epithelium (E). Mucous para-urethral glands (glands of Littré) are also visible (G). *(X55)*

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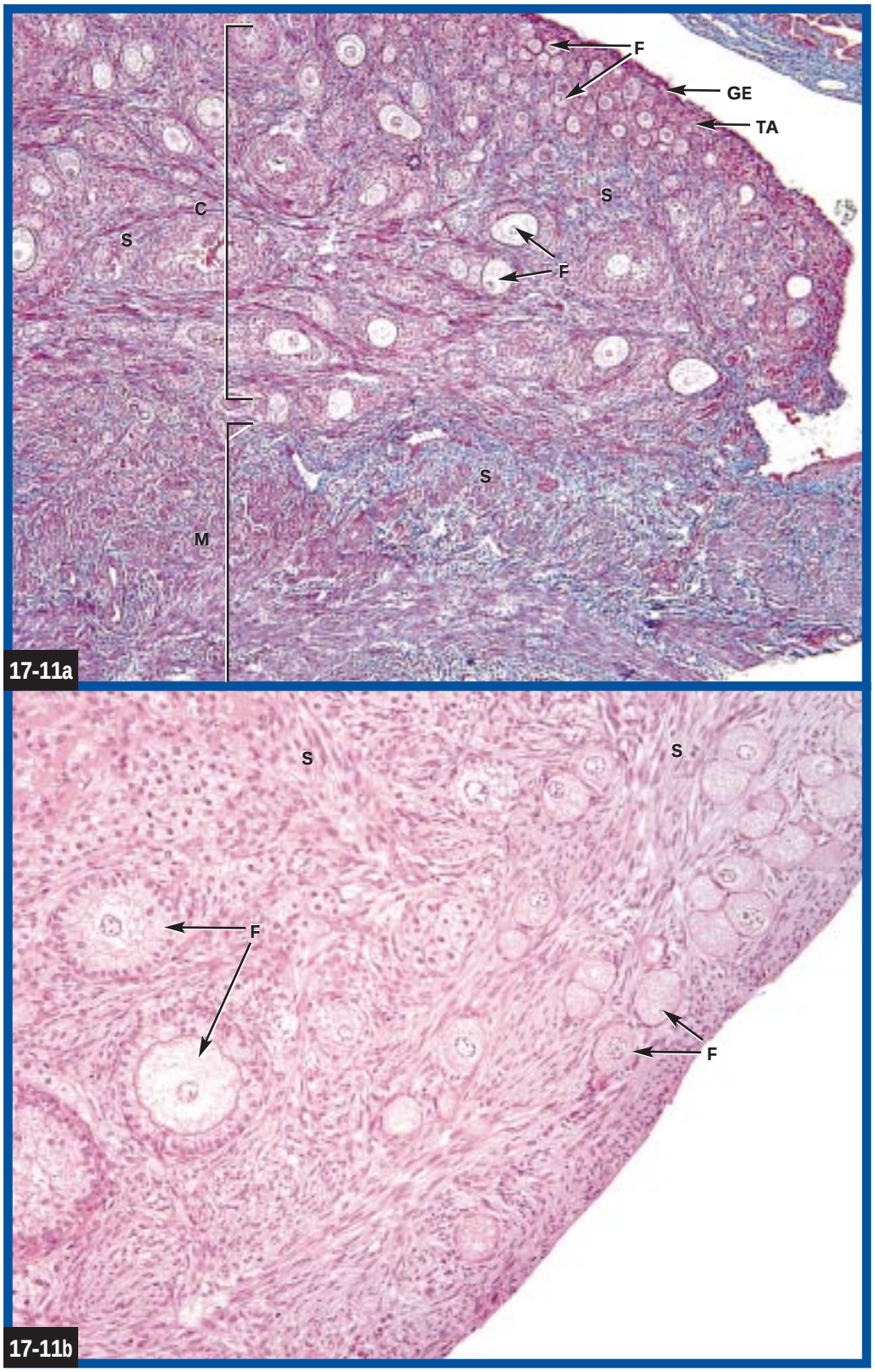

THE OVARY The ovary is covered with a germinal epithelium (GE), which is actually peritoneum, overlying a connective tissue tunica albuginea (TA). The bulk of the ovary is filled with connective tissue stroma (S), which is divided into a cortex (C) and a medulla (M). The cortical region is characterized by ovarian follicles (F), which are absent in the medulla. (a) This is a section of cat ovary. *(X65)* (b) Shown in this micrograph is the ovarian cortex with follicles in various stages of development. *(X130)*

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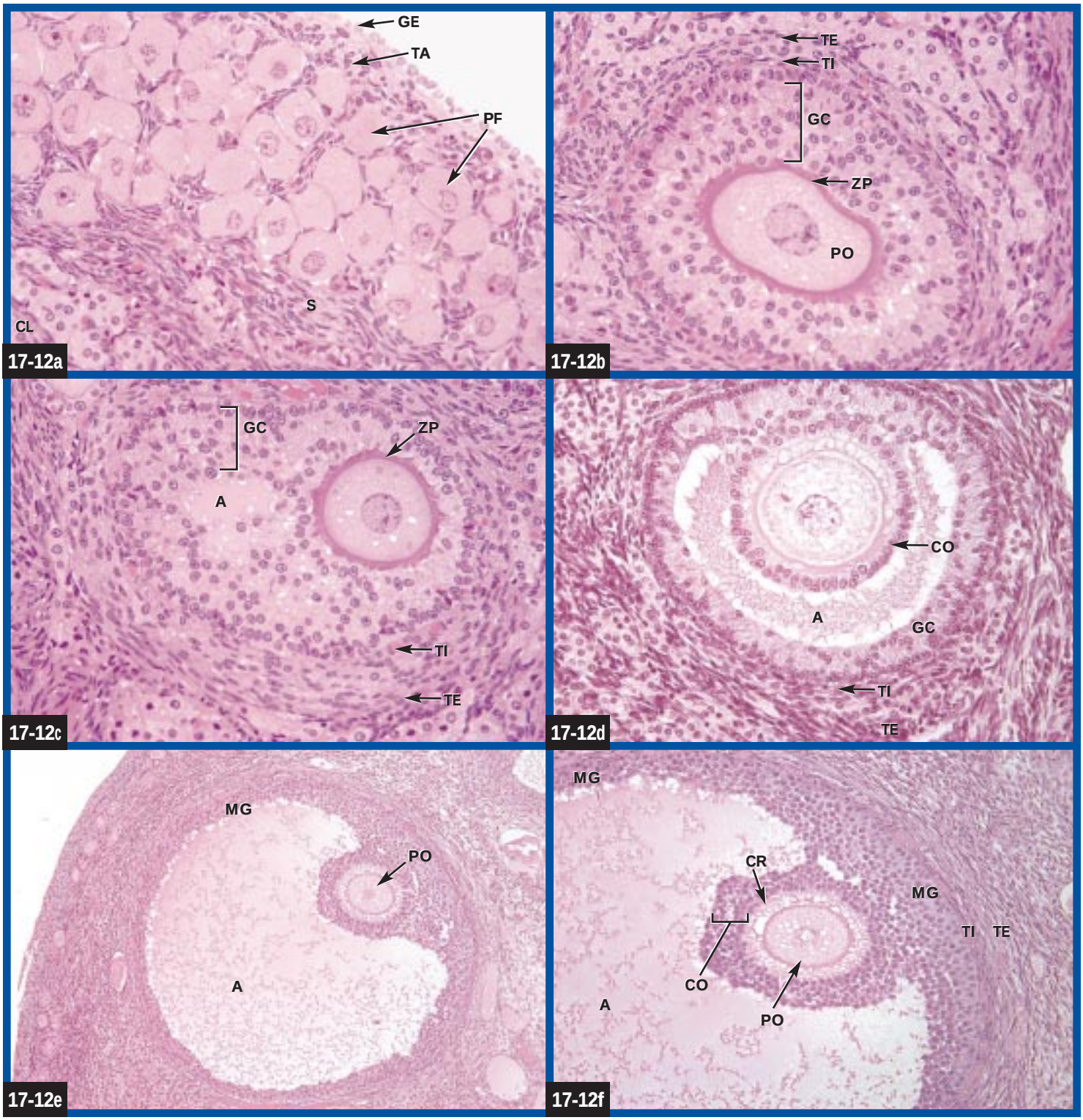

OVARIAN FOLLICLE DEVELOPMENT For reference purposes, be advised that the ovum stays the same size in all stages of development. (a) A layer of primordial follicles (PF) is found deep to the tunica albuginea (TA) and germinal epithelium (GE) of the ovary. A single layer of flat cells surrounds each primordial follicle. A corpus luteum (CL) and the stroma (S) are also visible. *(X220)* (b) In this multilaminar primary follicle, there are several layers of granulosa cells (GC) separated from the primary oocyte (PO) by the amorphous zona pellucida (ZP). A vascular and cellular theca interna (TI) and the fibrous theca externa (TE) have begun to develop in the stroma. *(X220)* (c) The antrum (A) has begun to develop in this secondary follicle and is filled with liquor folliculi, the diagnostic feature of a secondary follicle. Notice the more advanced state of the theca interna (TI) and theca externa (TE). *(X210)* (d) In this secondary follicle, the cumulus oophorus (CO) is starting to develop. *(X190)* (e) This micrograph shows a mature Graafian follicle. At this point, the primary oocyte is about to complete the first meiotic division. Note the well-developed antrum and membrana granulosa (MG). *(X50)* (f) In this micrograph, the primary oocyte and cumulus oophorus are starting to detach from the membrana granulosa in preparation for ovulation. The cells next to the primary oocyte form the corona radiata (CR). The theca interna and theca externa are also visible. *(X95)*

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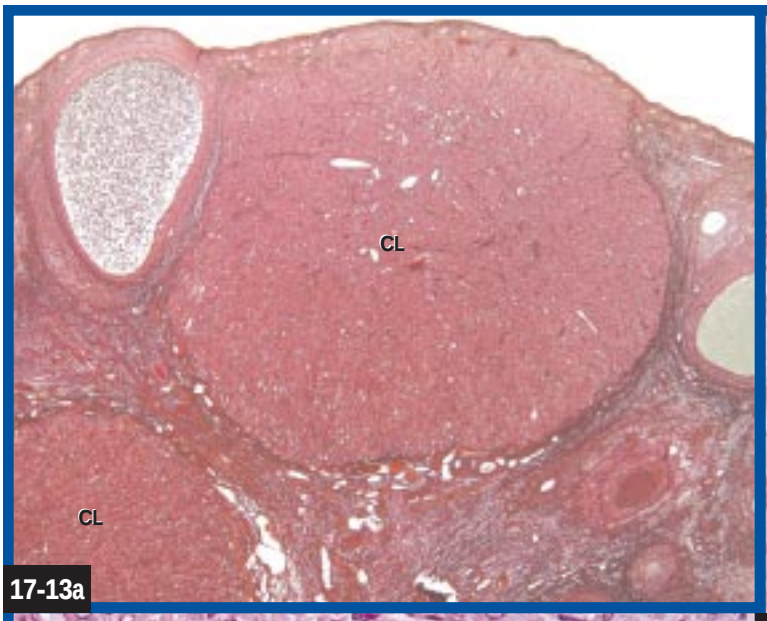
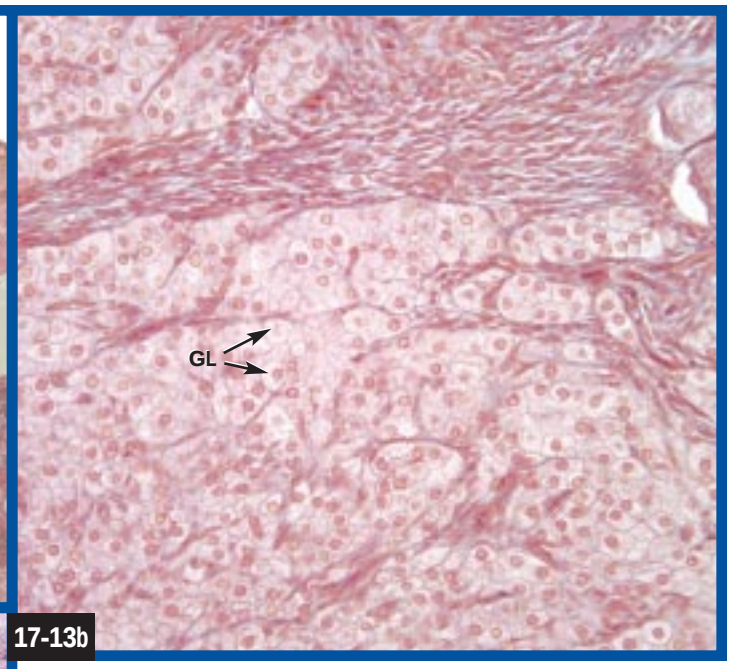
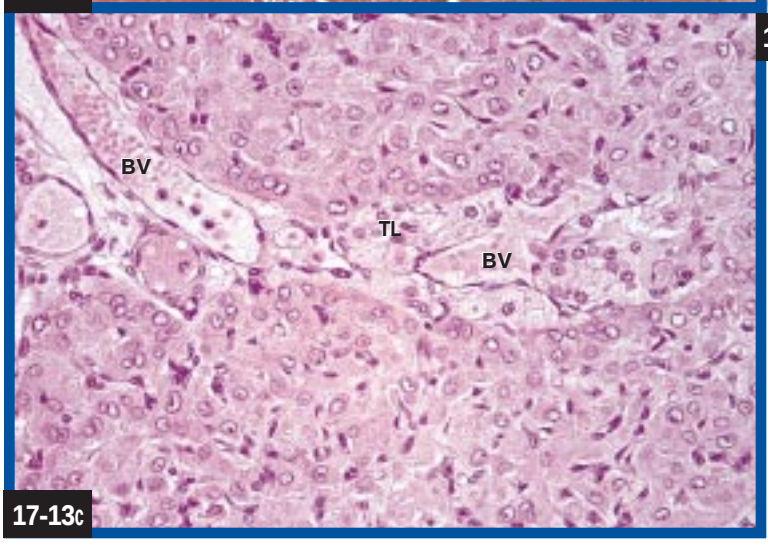
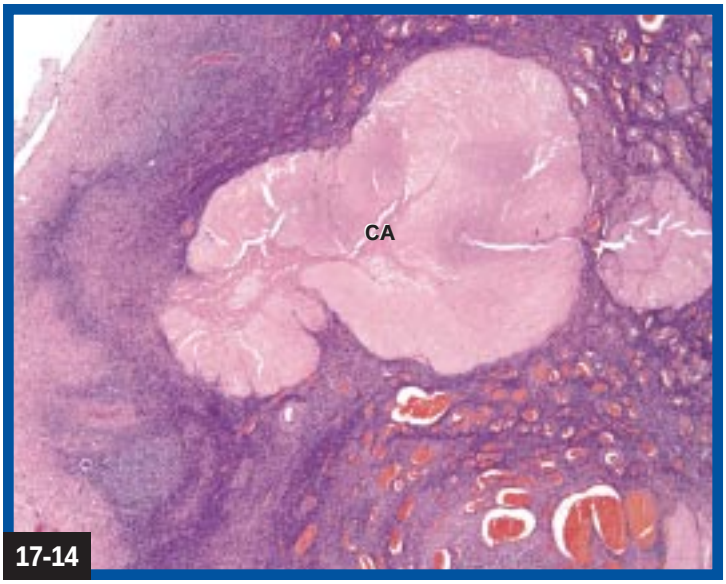


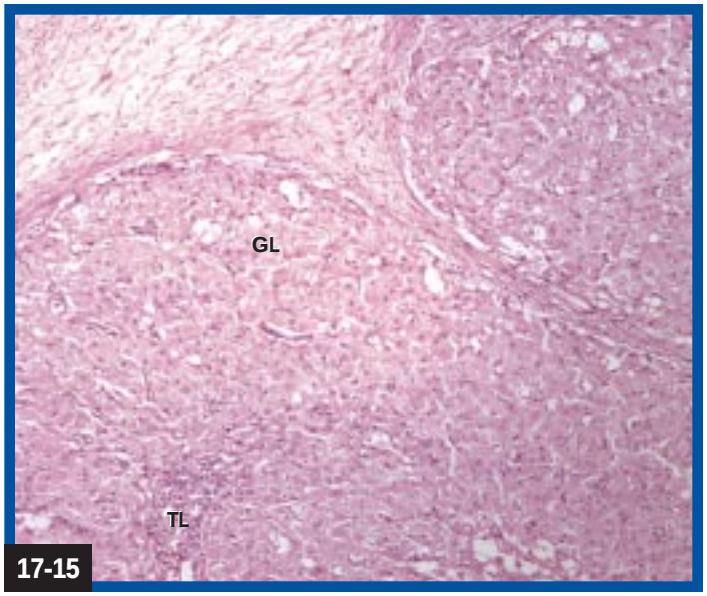




CORPUS LUTEUM The corpus luteum (CL) develops from the membrana granulosa, which forms the granulosa-lutein (GL) cells, and the theca interna, which contributes theca-lutein (TL) cells. Granulosa-lutein cells are large and pale staining. The less abundant theca-lutein cells are smaller and darker staining than the granulosa cells. They tend to be located near the periphery of the corpus luteum. (a) In this panoramic view, the large size of the corpus luteum is apparent. A second corpus luteum is visible in the lower left of the field. (*X20*) (b) The large granulosa-lutein cells are visible in this micrograph. (*X210*) (c) Blood vessels (BV) and a few theca-lutein cells are visible in this corpus luteum. (*X210*)



CORPUS ALBICANS After it has served its purpose, the corpus luteum is invaded by fibroblasts, the luteal cells undergo autolysis, and a corpus albicans (CA) is formed. *(X20)*



CORPUS LUTEUM OF PREGNANCY The corpus luteum of pregnancy continues to grow and develop. It remains functional for the first few months of pregnancy. In this micrograph, a portion of the corpus luteum is shown. Granulosa-lutein cells (GL) and theca-lutein cells (TL) are visible. *(X50)*

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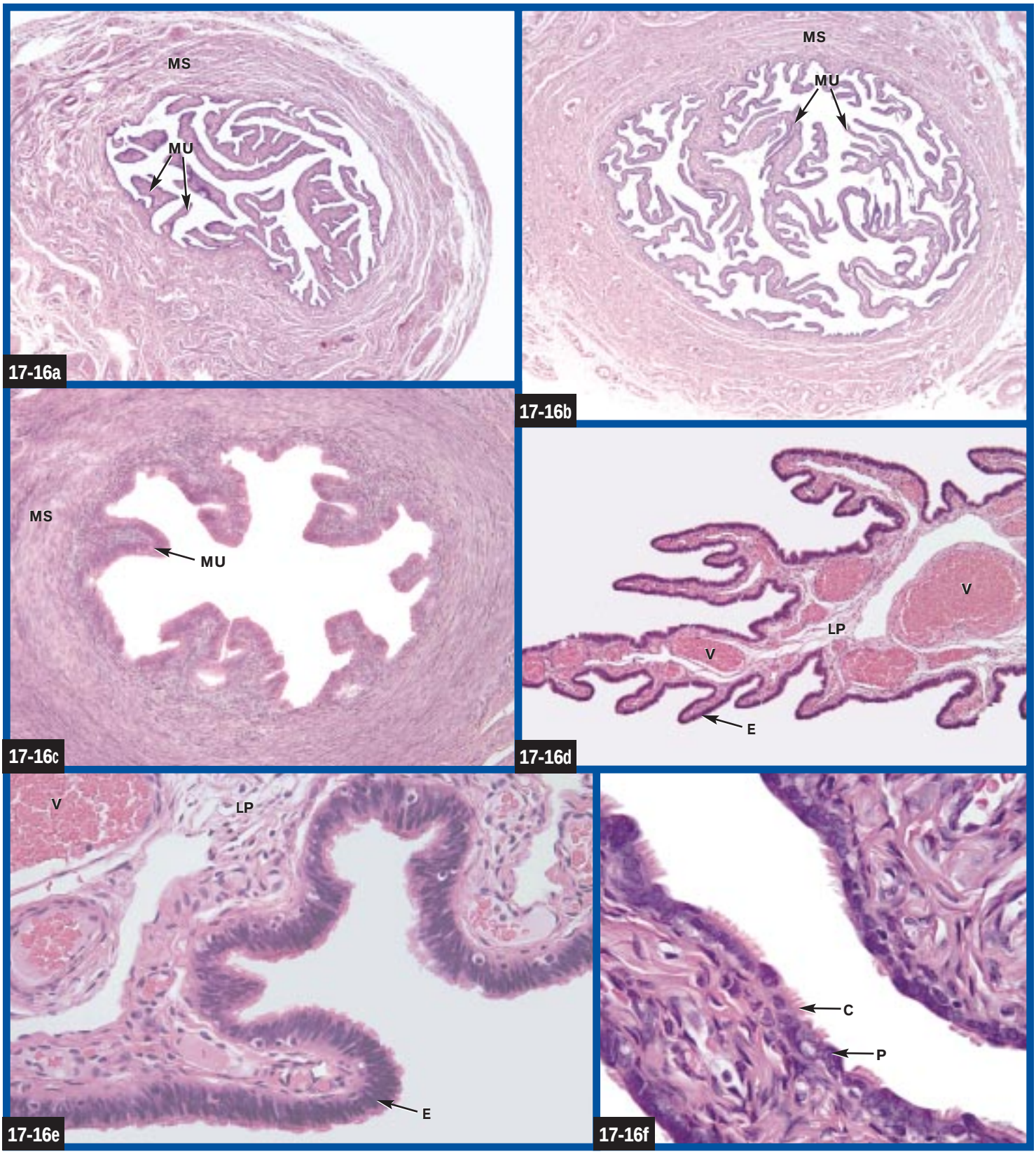

FALLOPIAN TUBES The Fallopian tubes are muscular structures extending laterally from the uterus. Their wall is made of a folded mucosa (MU), a muscularis (MS) consisting of poorly defined inner circular and outer longitudinal smooth muscle layers, and a serosa made of parietal peritoneum. Micrograph (a) is from the infundibulum, (b) is from the ampulla, and (c) is from the isthmus. These show that the mucosal folding is most intricate in the ampulla. (a) and (b) are *X20*; (c) is *X110*. Micrographs (d) and (e) are of fimbriae, the fingerlike projections extending from the infundibulum that assist in capturing the ovum at ovulation. The ciliated epithelium (E) sweeps into the Fallopian tube. Note the abundant, large veins (V) in the lamina propria (LP). Micrograph (d) is *X50*; (e) is *X230*. Micrograph (f) illustrates the epithelium made of ciliated cells (C) and nonciliated peg cells (P). *(X400)*

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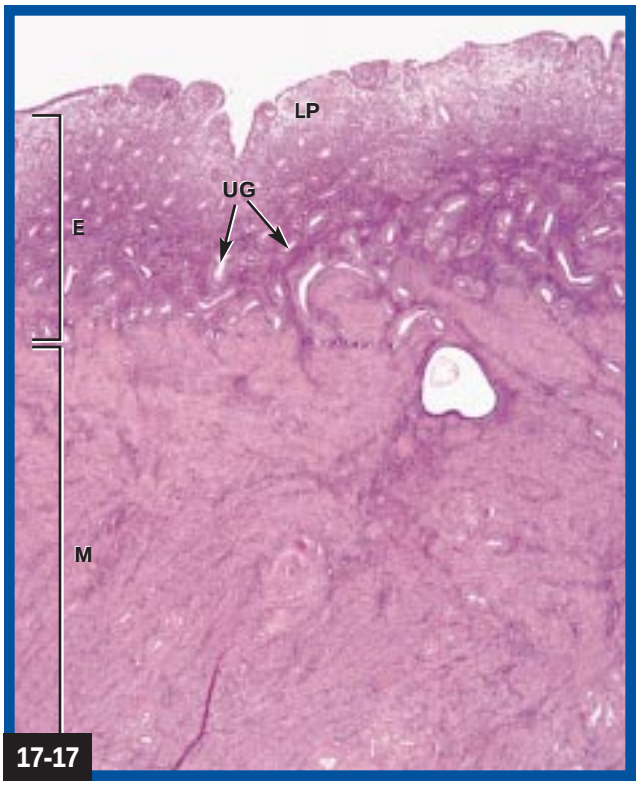
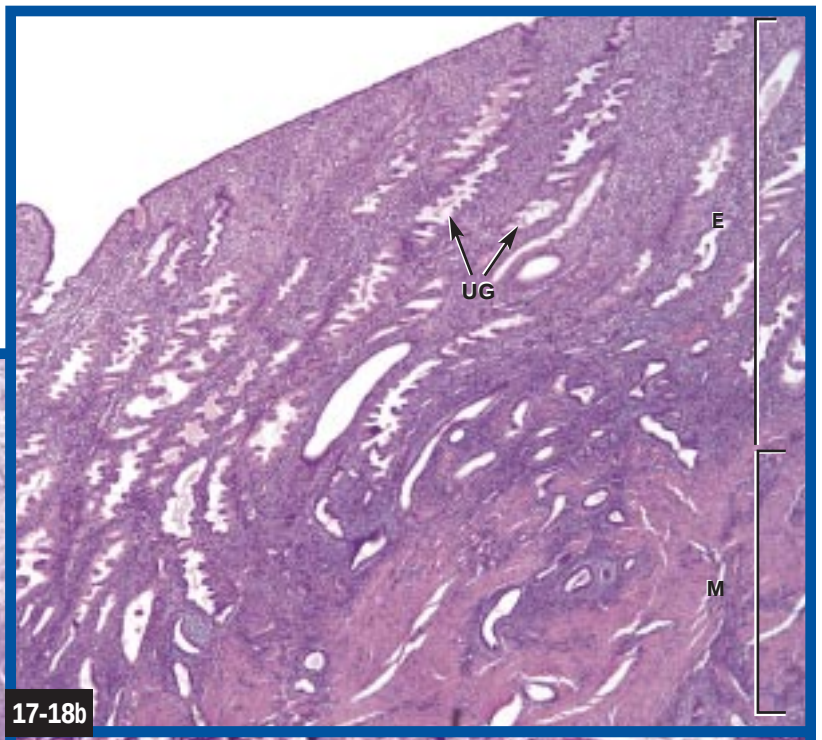
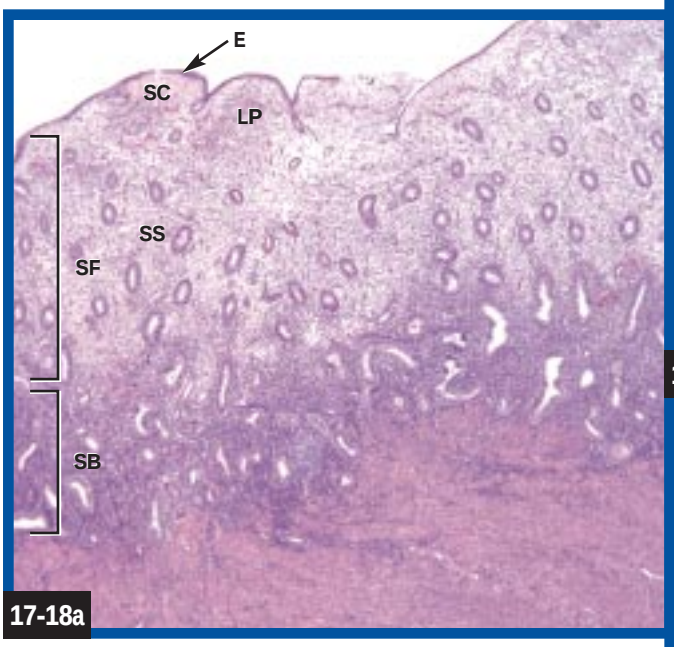
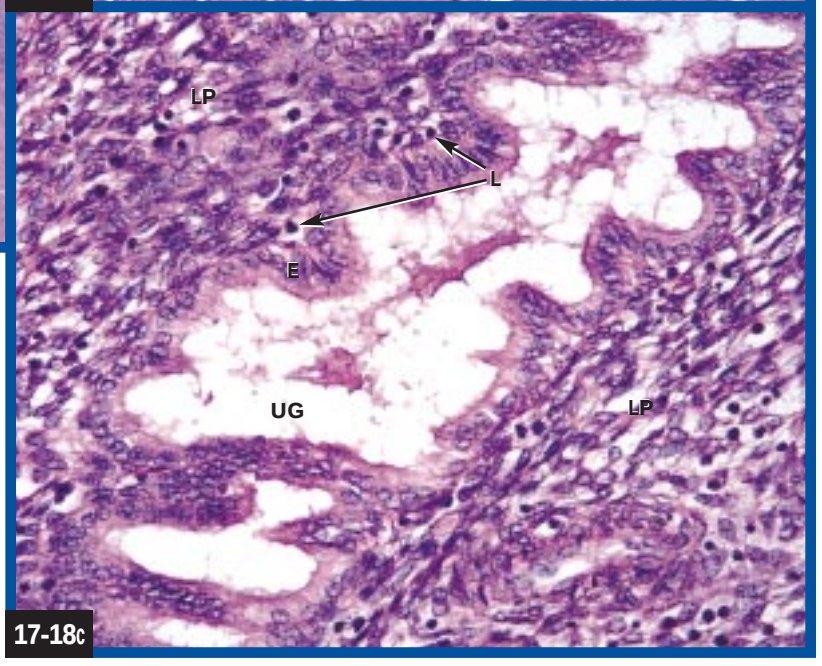


UTERUS This micrograph shows the uterine wall. Uterine glands (UG) penetrate the lamina propria (LP) of the endometrium (E). The thick myometrium (M) with its poorly organized smooth muscle layers is also seen. The perimetrium, made of serous membrane, is not visible in this preparation. *(X25)*







ENDOMETRIUM The endometrium is lined by a simple columnar epithelium (E) supported by a dense fibrous lamina propria (LP). Two endometrial layers are recognized. These are the basal stratum basalis (SB) and the more superficial stratum functionalis (SF), itself made of the stratum compactum (SC) and the stratum spongiosum (SS). During the menstrual cycle, the endometrium grows thicker, becomes more vascular, and the glands become coiled. (a) This micrograph shows the endometrium in the proliferative (follicular) phase of the menstrual cycle. Note the few, straight glands (UG). *(X20)* (b) The glands are more coiled in this micrograph of the endometrium during the secretory (luteal) phase. *(X25)* (c) A coiled gland is shown in this micrograph. Note the cellular lamina propria and the dark staining lymphocytes (L). *(X230)*

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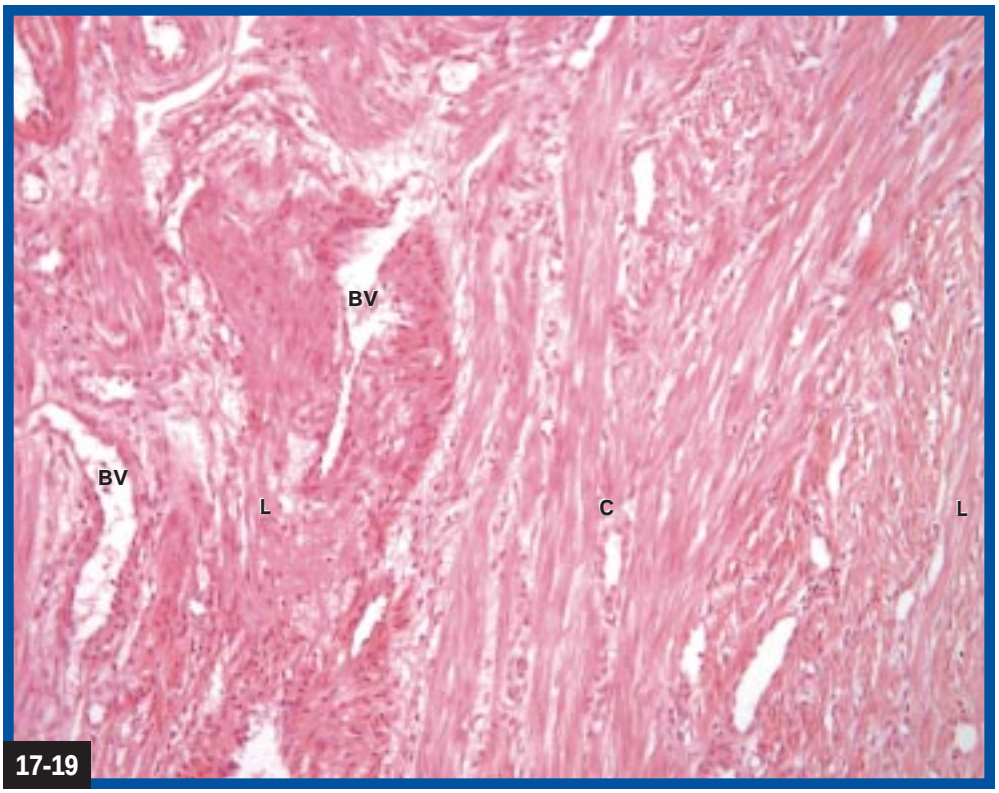
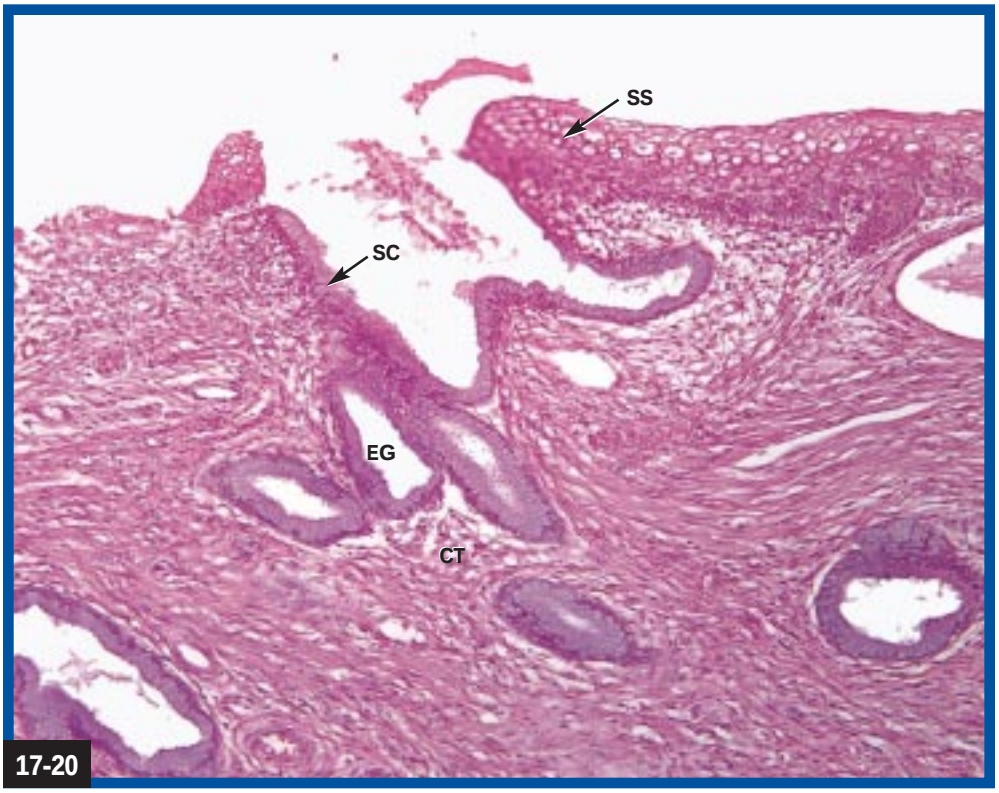


MYOMETRIUM The smooth muscle of the myometrium is arranged into poorly defined inner and outer longitudinal layers (L), separated by a vascular middle circular layer (C). This micrograph shows muscle fibers in both orientations as well as a few blood vessels (BV) and connective tissue (CT). *(X130)*



CERVIX The endocervical canal is lined by a simple columnar epithelium (SC), which secretes mucus, but it changes to a nonkeratinized stratified squamous epithelium (SS) where it projects into the vagina as the ectocervix. Endocervical glands (EG) are also visible. Deep to the epithelium is a dense elastic connective tissue layer (CT) with a few smooth muscle cells. *(X130)*

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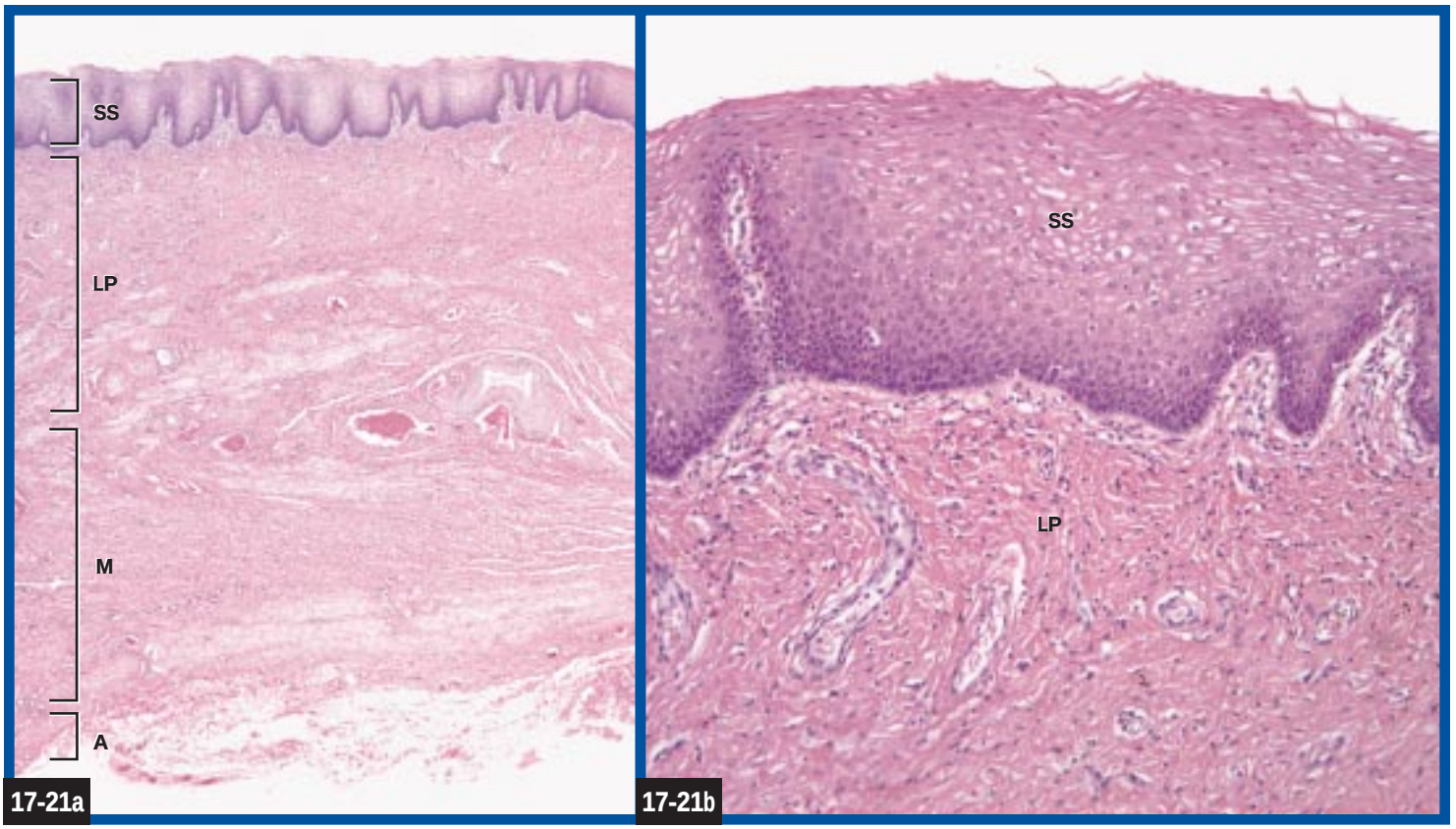
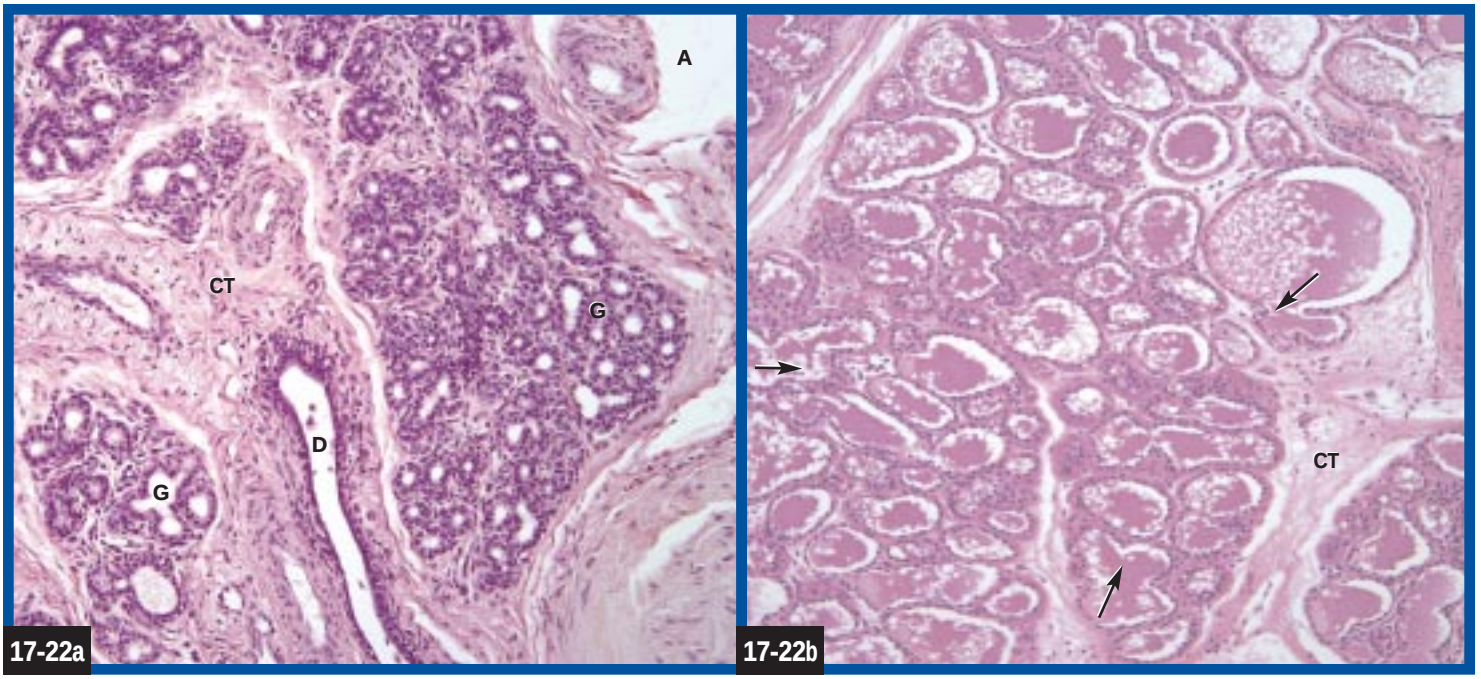


VAGINA The vagina consists of a mucosa, muscularis, and an adventitia. The mucosa is made of a nonkeratinized stratified squamous epithelium (SS) and is supported by a thick, fibrous, and elastic lamina propria (LP). Longitudinal and circular smooth muscle fibers comprise the muscularis (M), but the layers are not well-defined. An outer fibrous adventitia (A) blends with surrounding structures. (a) *X25* (b) *X130*



BREAST The mammary glands are compound tubulo-acinar glands occupying the approximately 20 lobes in each breast. (a) This micrograph is of inactive mammary glands (G). A duct (D), interlobar connective tissue (CT), and adipose tissue (A) are also visible. Note the absence of secretion in the glands. *(X110)* (b) The branching glands (arrows) are apparent in this active mammary gland. Note the secretion in the glands and the interlobar connective tissue. *(X110)*

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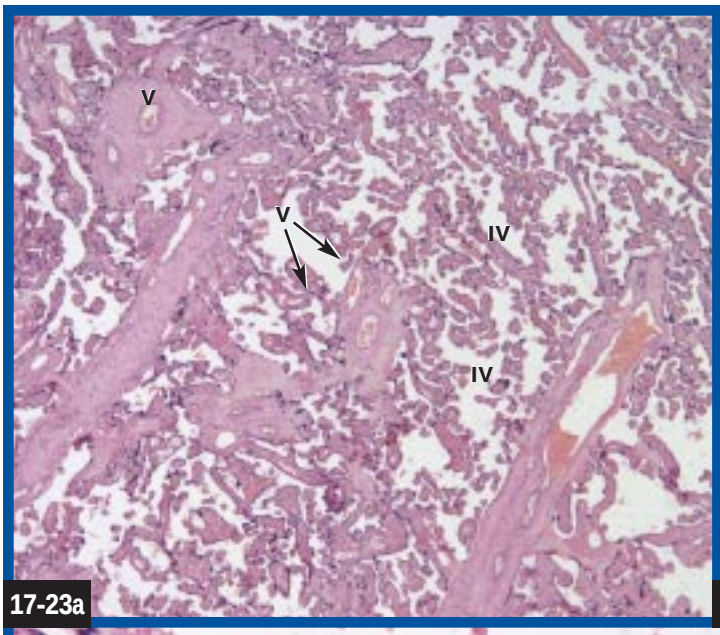
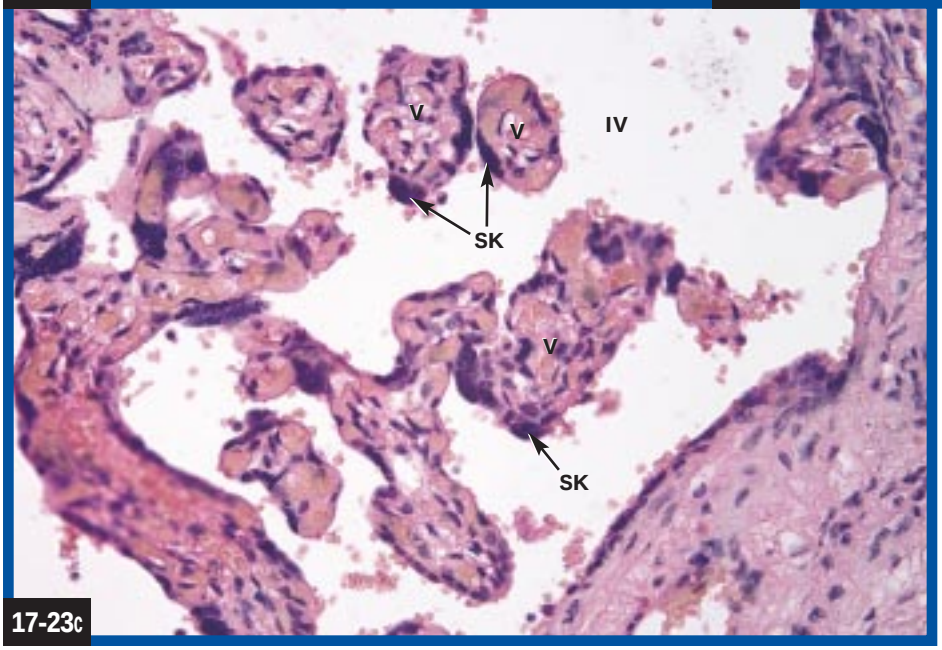


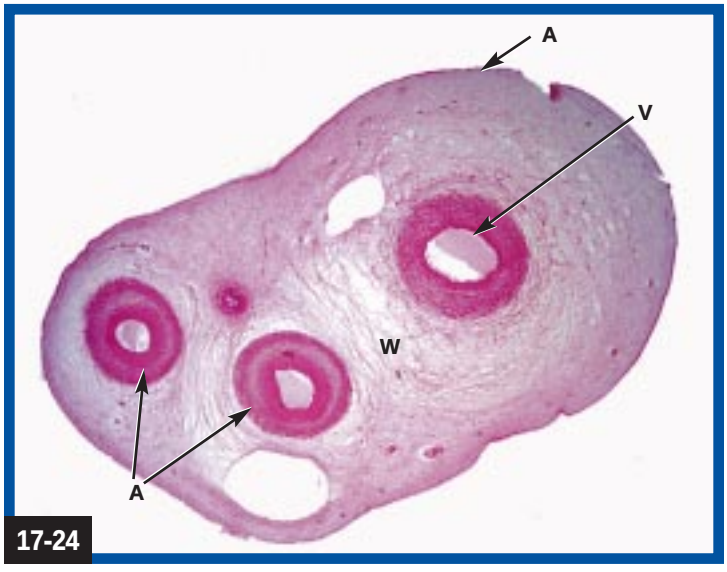
17-23a

17-23b



17-23c

PLACENTA (a) This micrograph is a panoramic view of the placenta. Large and small chorionic villi (V) and intervillous spaces (IV) are visible. Note the branching of the smallest villi. *(X20)* (b) In this cross section of a villus, the trophoblast layer (T), connective tissue (CT), and fetal blood vessels (BV) are seen. Maternal blood is found in the intervillous space (IV). *(X555)* (c) Clusters of syncytial trophoblast nuclei form clusters called syncytial knots (SK). *(X245)*



17-24

UMBILICAL CORD This umbilical cord has been cut in cross section. The two umbilical arteries (A) and the single umbilical vein (V) are surrounded by mesenchymal tissue called Wharton's jelly (W). The outer surface is covered with amniotic membrane (A). *(X8)*

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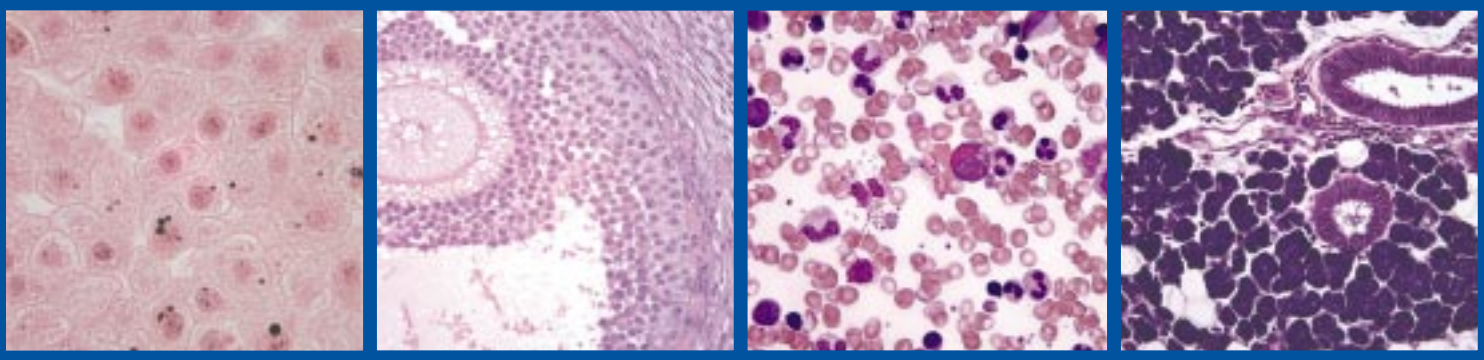
Further Reading



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